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Revisión

Multidisciplinary care in cystic fibrosis; a clinical-nutrition review

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Abstract

The multidisciplinary care, at different referral centers of cystic fibrosis, is aimed at monitoring and treating cystic fibrosis patients. Mortality attributed to this hereditary disease is high, since it affects the exocrine glands, involving multiple organs, and evolves in a chronic, progressive way. However, systemized care and the improved, shared understanding of gastroenterologists, nutritionists and pulmonologists, contribute to prolonged survival and abated morbimortality. The aim of this study is to describe the main aspects of clinical and nutritional intervention in cystic fibrosis patients so that monitoring by a multidisciplinary team is optimized and performed as early as possible. The review was carried out on articles indexed in the Medline, Lilacs, SciELO, Current Contents and Cochrane databases, finding 189 articles in Portuguese, English and Spanish, with emphasis on articles published between 2000 and 2011. Due to the scientific relevant contribution, some publications before 2000 were included totalized 77 related to the multidisciplinary care. The reviewed studies suggest that multidisciplinary care is essential for knowledge integration in order to impose permanent update of scientific information, thereby contributing to the development of intervention strategies that enhance survival and motivate the development of skills to cope with the complex treatment regimen that is necessary for cystic fibrosis treatment and prevention of related complications.

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Key words: *Cystic fibrosis. Lung disease. Nutritional status. Neonatal screening. Spirometry.*

ATENCIÓN MULTIDISCIPLINARIA EN LA FIBROSIS QUÍSTICA; UNA REVISIÓN CLÍNICA Y NUTRICIONAL

Resumen

La atención multidisciplinaria, en diferentes centros de referencia de la fibrosis quística, tiene por objeto el seguimiento y el tratamiento de pacientes con fibrosis quística. La mortalidad atribuidas a esta enfermedad hereditaria es alto, ya que afecta las glándulas exocrinas, afecta múltiples órganos, y evoluciona de manera crónica y progresiva. Sin embargo, la atención sistematizada y la mejor comprensión compartida de los gastroenterólogos, nutricionistas y neumólogos, contribuir a la prolongación de la supervivencia y la morbi-mortalidad disminuyó. El objetivo de este estudio es describir los principales aspectos de la intervención clínica y nutricional en pacientes con fibrosis quística, para que la supervisión de un equipo multidisciplinario se optimiza y realiza lo más pronto posible. La revisión se llevó a cabo en artículos indexados en el Medline, Lilacs, SciELO, Current Contents y bases de datos Cochrane, la búsqueda de 189 artículos en Portugués, Inglés y Español, con énfasis en los artículos publicados entre 2000 y 2011. Debido a la destacada contribución científica, algunas publicaciones antes de 2000 se incluyeron totalizado 77 relacionados con la atención multidisciplinaria. Los estudios revisados sugieren que la atención multidisciplinaria es esencial para la integración del conocimiento con el fin de imponer actualización permanente de información científica, contribuyendo así al desarrollo de estrategias de intervención que mejoren la supervivencia y motivar el desarrollo de habilidades para hacer frente a la pauta de tratamiento complejo que es necesario para tratamiento de la fibrosis quística y la prevención de las complicaciones relacionadas.

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Palabras clave: *Fibrosis quística. Enfermedad pulmonar. Estado nutricional. Detección neonatal. Espirometría.*

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Abbreviations

CF: Cystic fibrosis.
CFTR: Cystic fibrosis transmembrane conductance regulator.
EL-1: Faecal elastase-1.
IRT: Immunoreactive trypsin.
GER: Gastroesophageal reflux.
PTH: Parathyroid hormone.
BMD: Bone mineral density.
PG: Prostaglandin secretion.
IGF: Insulin-like growth factor.
REE: Resting energy expenditure.
RDA: Recommended dietary allowances.
CFF: Cystic fibrosis foundation.
FVC: Forced vital capacity.
FEV1: Forced expiratory volume in one second.

Introduction

Cystic Fibrosis (CF) is a disease that reduces life span and has high morbidity.[1] Despite therapeutic advances and increased survival, patients with CF often experience decreased lung function, malnutrition and pancreatic insufficiency among other complications.[2] New treatments offer hope, but also present challenges for patients, practitioners and researchers.[3]

The study by Farrel[4] combined a variety of methods to determine the prevalence of cystic fibrosis in the European Union. The results of literature reviews, surveys, and registry analyses revealed a mean prevalence of 0.737/10,000 in the 27 European Union countries, which is similar to the value of 0.797 in the United States, and only one outlier, namely the Republic of Ireland at 2.98.

CF is more common among white people although present all racial and ethnic groups.[5]

Combined multidisciplinary care at CF Centers and aggressive treatment of pulmonary symptoms with careful attention to nutritional well-being have substantially improved life expectancy in the past 10 years.[6]

This paper aims to describe the main aspects related to the clinical and nutritional management of cystic fibrosis patients so that individual coaching is optimized and carried out at early stages. The adoption of such management guidelines at reference centers is necessary in order to maintain standard care service in centers equipped with multidisciplinary teams. The review was conducted on journal articles indexed in the Medline, Lilacs, SciELO, Current Contents and Cochrane databases, finding 189 articles when using cystic fibrosis, lung disease, nutritional status, neonatal screening and spirometry as key words, described in Portuguese, English and Spanish, with emphasis on articles published from 2000 to 2011.Due to the scientific relevant contribution, some publications before 2000 were included totalized 77 related to the multidisciplinary care.

Genetics

CF is an autosomal recessive disorder that affects the exocrine glands, involving multiple organs, and evolves in a chronic and progressive way.[7] When each parent has one CF gene, the risk in each pregnancy of the child being born with or without the disease is 25% and 75% respectively, and the probability of being born healthy, but with one CF gene, is 50%.[8]

The CF gene is located on the long arm of chromosome 7, consists of 250 kilobase DNA fragments, and has the ability to encode a 6.5 kb mRNA, which transcribes a transmembrane protein, an ion transport regulator, consisting of 1,480 amino acids, known as CFTR (Cystic Fibrosis Transmembrane Conductance Regulator).The CFTR is essential for the transport of ions through the cell membrane and is involved in the flow of chlorine, sodium and water. More than 1,600 mutations in the CFTR gene, however the most common of these occurs through a deletion of three base pairs, resulting in the loss of an amino acid (phenylalanine) at position F508 del of the CFTR protein which impedes proper functioning and thickening of secretions.[8]

Disease manifestations are due to changes in the CFTR function, thus resulting in mild and more severe chronic lung disease manifestations, chronic diarrhea and steatorrhea, difficulty in gaining weight and height.[9]

Cystic fibrosis diagnosis

According to the Cystic Fibrosis Foundation, in order to diagnose cystic fibrosis[10] one or more clinical manifestations must be considered such as obstructive/suppurative lung disease or chronic sinusits, gastrointestinal and nutritional changes, salt loss syndrome, urogenital abnormalities resulting in azoospermya associated with identification of two mutations for cystic fibrosis or sweat chloride ≥ 60 mmol/L in two dosages. Also the family history of CF, demonstration of abnormal ion transport in nasal epithelium or neonatal screening test by the trypsin method[9,10] should be considered. The clinical evaluation of not classic or doubtful FC cases may be performed through rectal biopsy which is well tolerated by young infants e not require general anaesthesia or sedation.[11-14]

Population screening programs for newborns were imposed because the need for early treatment and improved of clinical. The screening is done simultaneously with the other constants in newborn screening, by immunoreactive trypsin blood tested. Cases screened as positive, do not give a definite diagnosis, because there is substantial proportion of false-positive. Confirmation is performed by genetic analysis of DNA from suspected patient.[8]

In CF patients the assessment of exocrine pancreatic function is a mandatory procedure for diagnosis. The measure of faecal elatase-1(EL-1) has shown promise in early treatment of children after neonatal screening,

it is an indirect test, accurate and reproducible pancreatic function whose values are reliable in a small sample of faeces.[15]

Since the early use of screening tests, there is controversy as to the real impact on the progression of the disease, beyond the cost-effective aspect. However, those diagnosed through neonatal screening had a better evolution of nutrition and growth, and better lung function values at 10 years of age.[9,16]

In recent years there has been increased survival of CF patients due to research and scientific advances that have enabled a better understanding of the disease also the inclusion of serum immunoreactive trypsin (IRT) in neonatal screening.[17]

Clinical manifestations

The diseases of genetic origin is characterized by exocrine gland dysfunction, including pancreas, sweat glands and mucous glands of the respiratory tract, gastrointestinal and reproductive systems.The involvement of the respiratory system is considered the most critical in severity and lethality. Usually patients present a combination of diarrhea, recurrent respiratory infections and weight and height defficiency. There are less common manifestations, of which, the most important is meconium ileus.[6,9]

CFTR dysfunction impairs hydroelectric epithelial transport causes alterations to viscoelastics mucus proteins and provides greater susceptibility to respiratory infections such as pneumonia, bronchitis, bronchiectasis and rhinosinusitis.[11]

CF patients have great susceptibility to colonization and endobronchial infection by specific bacteria, the chronic bronchopulmonary infection being the major cause of progressive lung damage in cystic fibrosis. In the first years of life, the respiratory tract of patients is usually colonized with Staphylococcus aureus. Then comes colonization by Pseudomonas aeruginosa, wich is usually related to the progression of lung disease. Recent studies have shown that the prevalence of P. aeruginosa in the first years of life is high, but generally nonmucoid strains are detected. Pseudomonas aeruginosa is the most common pathogene, infecting approximately 80% of the population, however, variations may occur between percentage fibrocystics .Over the years, Pseudomonas changes its phenotype has changed and started producing large quantities of a substance (polysaccharide polymer) called alginate, when it becomes known as mucoid strain. This morphology is pathognomonic of cystic fibrosis.[12]

Alginate facilitates bacterial, adherence to airways and the formation of microcolonies, hindering opsonization, phagocytosis and the penetration of antibodies and antibiotics. This bacterial phenotype is associated to a major difficulty in eradicating the infection, which becomes chronic and generates an intense inflammatory response. With advancing age, 70-90% of patients are infected by P. aeruginosa. Other agents such as Haemophilus influenzae and Burkholderia cepacia can also colonize the respiratory tracts. The latter is related to a more serious prognosis and hematogenous dissemination in addition to death called "cepacia syndrome".[18]

The presence of active CFTR in intestinal epithelium predicts that the gastrointestinal tract will be a site of disease. The gastrointestinal manifestations are most often the first changes in CF**,** may also occur in intrauterine life and mostly secondary to pancreatic insufficiency or gastric motility disorders. Obstruction of pancreatic canaliculi by mucus plugs impedes the release of enzymes into the duodenum, determining poor digestion of fats, protein and carbohydrates.[19] Bulky stools, greasy and pale are resulting from poor digestion and protein calorie malnutrition marked by loss of nutrients, and other factors inherent in the cystic fibrosis.[20]

Malabsorption is predominantly caused by epithelial dysfunction, resulting from rejection of nutrients not hydrolyzed in the lumen due to pancreatic insufficiency. In 85% of CF patients, the pancreas does not produce sufficient enzymes for complete digestion of ingested food and one of the first signs is the malabsorption of nutrients.[21] The proteins required for growth and body tissue replacement are not fully used. Fat, the most energetic nutrient, is not absorved growth is delayed and liposoluble vitamin deficiencies may appear.[22]

Patients who have pancreatic insufficiency have worse prognosis than who are pancreatic sufficient,but whether this is because of nutritional deficits or because the CFTR deficit is more severe is uncertain[23,24].

Gastroesophageal reflux (GER) is common in CF and several factors likely contribute including large meals and medications that reduce lower esophageal sphincter. GER symptoms are present in a majority of patients and may worsen the respiratory condition.[25] The contribution of GER disease to the progression of pulmonary disease in CF is uncertain,but many physicians are vigorous in their treatment in part because of the possibility that there is some exacerbation associated with it.[23]

The first manifestation of pancreatic failure in cystic fibrosis is meconium ileus —obstruction of the terminal ileum by thick meconium— which appears in 15-20% of infants and most diagnoses of meconium ileus (90%) are cystic fibrosis related. The pathogenesis has been linked to impaired secretion of pancreatic enzymes and poor digestion and dehydration of intestinal contents in the uterus, resulting in dried hiper viscose meconium which leads to obstruction at the distal ileum level. The distal intestinal obstruction syndrome or meconium ileus equivalent occurs in about 20% of patients, usually adolescents and adults.[26]

Van der Doef et al.[27] determined the prevalence, risk factors and treatment of constipation in patients with CF in a cohort of 214 patients and have associated the occurrence of this diagnosis with low absorption of

total fat and a history of meconium ileus. There was no association with the use of integrated fiber and fluid intakes.

Rectal prolapse occurs in about 20% of patients, especially those under two years of age. Contributing factors for this occurrence are bulky viscous stools which adhere to rectal mucosa, loss of peri-rectal fat, decreased muscle tone due to malnutrition added to increased intra-abdominal pressure by coughing. Resolution is usually spontaneous with the use of pancreatic enzymes and the improvement of the nutritional status.[28]

CF affects the liver in different ways. Due to change in the CFTR protein, occurs a decrease insecretory function the bile duct epithelium making thicker secretions, this would lead to obstruction of bile ducts. This obstruction would lead to gradual changes in the liver may even get to cirrhosis.[17,23]

Most cystic fibrosis patients develop some level of liver disease, which may include elevated transaminases, hepatosteatosis or biliary tract diseases. Hepatosteatosis is common in 20-60% of patients. Cholelithiasis is often diagnosed as well and 15% of adults have gallstone. Liver diseases are mentioned as major causes of death among CF patients.[12, 29] According Nash et al.[30] liver disease detected and closely monitored in adults appeared to have a milder course than childhood CF.

Liver lesion results in damage to the endogenous synthesis of vitamin D and its metabolism, and may bring about bone disease and changes in calcium metabolism, being that, intestinal absorption of this mineral is made under the influence of vitamin D. The low serum levels of 25 (OH) vitamin D contribute to the release of parathyroid hormone (PTH) with the goal of raising calcium levels, but high levels of this hormone mobilize calcium and phosphorus from the bones, further decreasing bone mass Several studies have shown low bone mineral density (BMD) in patients with CF.[24,31]

Feijó et al,[31] found patients with low BMD, even in childhood. In the adult group, almost all had involvement in bone mineral density; 72% had osteopenia and 14% had osteoporosis osteoporosis. No correlation was observed between bone status, FEV 1 and the presence of F508 del mutation. Actually, the pathogenesis of such low BMD is not completely understood. A variety of potential risk factors may contribute to the development of osteoporosis in these patients, such as malnutrition, pancreatic insufficiency, calcium malabsorption, physical inactivity, corticosteroid therapy, chronic respiratory acidosis, reduced levels of sex hormones and decreased levels of insulin associated to diabetes.[24]

A recent analysis has suggested that loss of CFTR activity may result in the increased resorption of bone cells in CF patients by means of a significant decrease of osteoprotegerin secretion (OPG-protein of TNF receptors superfamily that acts as a soluble inhibitor in the maturation and activation of osteoclasts) accompanied by increased prostaglandin secretion (PG) E2 in cultured osteoclasts.[32]

Cystic fibrosis-related diabetes mellitus (CFRD) is an increasingly common complication of cystic fibrosis and did not match any of the types 1 and 2 classic disease.A minority developed diabetes mellitus requiring drug treatment, but changes in subclinical increase with age. The prevalence of diabetes increases with age, reaching up 40%of the cases in patients older than 30 years and provide adverse effects on clinical status, nutrition and lung function.[33,34]

Ripa et al.[35] demonstrated the presence of glucose intolerance and impairment insulin secretion in a significant percentage of children with CF .The reduction in insulin secretion appears to be associated with impairment of growth possibly via reduction of the levels of the growth-promoting insulin-like growth factor (IGF) axis.

The physiological mechanism of glucose intolerance in CF is controversial. Initially the endocrine tissue of the pancreas is preserved, but with increasing patient age, cells are lost and the gland begins to be completely replaced by fibrous tissue. Changes of chloride channel lead to hyperviscosity of pancreatic duct secretion, causing obstructive lesions, fatty infiltration,progressive fibrosis of the islets and reduced secretion of insulin, glucagon and pancreatic polypeptide. The accumulation of amyloid substance inside beta cells, present in patients with CF and diabetes, but absent in nondiabetic CF patients, contributes to insulin deficiency due to respective cytotoxic and limiting effect of insulin secretion.[36]

Delayed puberty is a common fact mainly related to nutritional impairment of the patient and the effects that chronic illnesses have on the body. In patients with good nutritional status and controlled pulmonary disease, puberty occurs at the customary time. Sterility is present in 98% of male patients, due to obstruction of vas deferens, leading to obstructive azoospermia. Female fertility is reduced by 20-30%.[9]

Nutritional manifestations

CF patients have high caloric requirements due to an increased resting energy expenditure (REE) bacterial infection and malabsorption.[38] REE is higher in patients with more severe phenotype.[33,39] At rest, patients with moderate pulmonary disease may experience a slight increase basal energy metabolism and during exercise, total energy expenditure increases dramatically. In patients with severe disease, this spending also increased in the basal resting, due to lack of respiratory reserve .Possibly, patients with moderate pulmonary disease adapt to increased resting energy expenditure, reducing the level of physical activity.[40]

Growth deficiency and malnutrition occur primarily owing to the difficulty these patients have in achieving energy needs and energy losses caused by the disease, which are mainly due to chronic lung inflammation and infections, malabsorption caused by pancreatic insuffi-

ciency, decreased bile flow and lung inflammation .The hepatic manifestation is much less prevalent and reaches approximately one third of patients. The gene CFTR is expressed exclusively in the apical membrane of colangiocytes and the epithelium of the gall bladder and not in hepatocytes leading to cholestasis and periportal fibrosis.[38]

Malnutrition may be aggravated by the presence of anorexia, resulting from gastroesophageal reflux and/or cough, respiratory infections and chronic psychosocial stress. The role of dietary treatment is to improve or maintain adequate nutritional status of the patient and break the vicious malnutrition-infection cycle.[33]

It is recognized that CF patients require at least 120-150% of the energy established by the Recommended Dietary Alowances (RDA's)[41] published in 1989 for the same age and sex.Lung function and nutritional status are closely correlated, and the severe weight loss can lead to a decrease in lean body mass, with consequences on respiratory muscles.The protein-energy malnutrition is recognized as the worst prognostic factor of the disease.[42]

As a definition for patients with malnutrition or nutritional risk, the parameters used are weight, length, head circumference, body mass index, mid-arm circumference and skinfold thickness. These parameters used in accordance with standardized growth charts for age and gender, are essential for proper nutritional monitoring.[42]

The American Cystic Fibrosis Foundation (CFF) through the CFF Development Committee on Nutrition, has published a systematic review of evidence-based recommendations for the nutritional management of patients with CF. It highlights the difficulties of using the weight percentage in relation to ideal height and suggests the use of BMI percentile for children older than two years of age. For children under two, it is used the % weight for height percentile and weight for height.[10,42,43] Milla[1] showed that utilization of the BMI percentile was more accurate than the percentage of ideal weight for age, for the changes in forced expiratory volume in one second.

The nutritional follow up, at least at three months intervals, is essential to identify nutritional problems or altered eating habits. The use of three-day food records is recommended for caloric intake assessment, macronutrient proportion, timing, and use of supplements, enzymes and vitamins.[42,43]

In a cohort of 3298 patients 2 years old or older with cystic fibrosis, grouped by presence or absence of malnutrition, Steinkamp & Wiedemann found a statistically significant association between malnutrition, forced vital capacity (FVC), partial pressure of oxygen and of forced expiratory volume in one second (FEV1) ($p < 0.05$). This was also found between *Pseudomonas aeruginosa* and decreased lung function.[44]

Chronic bacterial infection of the respiratory tract by microorganisms as *Pseudomonas aeruginosa,* members of the *Burkholderia cepacia* complex or *Staphylococcus aureus,* cause destruction and loss of lung function and is closely related to nutritional status. A major cause of nutritional depletion is the increase in energy expenditure due to inflammation and lung infection.[8, 45]

In a longitudinal study aiming to evaluate the relationship between nutritional status and lung function, a strong association was found between FEV1, FVC and weight-height,height-age and body mass index ($p < 0.05$). Observed lung function was better in those with weight-height > 10th percentile, from 3 to 6 years, and lower for those with < 10th percentile.[46]

A survey conducted on outpatient care assessed the nutritional status, food consumption and values obtained by the Shwachman-Kulczycki score[47] in CF patients, observation noted that the weight-age , triceps skinfold thickness and body fat percentage increased significantly with the use of pancreatic enzymes and nutritional supplements ($p < 0.05$). Hamill et al.[48] conducted a nutritional assessment which involved taking measurements of weight, height by length, arm circumference and skinfold (triceps, biceps, subscapular and suprailiac).

These measurements were compared to growth charts Healths National Center for Healths Statistics and converted into scores based on age and gender.[49]

In this analysis, energy consumption increased in relation to RDA ($p < 0.05$) and there was statistically significant association between nutritional status and severity of pulmonary disease assessed by Shwachman-Kulczycki score ($p < 0.05$).[49]

This score consists of four criteria: general activity, physical examination, nutritional and radiological chest, scored on a scale of 5 to 25 points(best performance, highest score). The maximum score is 100 points and represents a patient with an excellent clinical.[47]

To assess nutritional status and establish an intervention plan, 16 patients, with an average of 8.15 years, were monitored in a cross-sectional study and observation attested a statistically significant difference between current and ideal weight ($p = 0.04$)[50]. In those age groups studied, 43.7% of patients had weight-height below the 10th percentile. The study showed that CF Nutrition Consensus[51,52] detected more cases of malnutrition in CF than the World Health Organization recommendation.[50-53]

The CF Nutrition Consensus carry out the assessment of nutritional status % by weight for age, body mass index and percentile weight for height allowing the identification of patients with normal weight at risk for nutritional failure and need for invasive support. The recommendations of the World Health Organization using percentiles of weight for height, weight for age, height for age and body mass index identifying the eutrophic and nutritional risk.[51-53]

Satisfactory results were found in a 2009 study that assessed the nutritional status and food intake. In a sample of 85 patients, between 6 and 18 years, 77% were eutrophic (BMI > p25) and average intake was at 124.5% of RDA. In the univariate logistic regression

analyses was found asignificant association between the independent variable calorie intake and the Z score for weightage. The multivariate analyses, based on the hospitalizations, demonstrated that a 1% increase in the calorie intake decreases the chance of having short stature by 2%(OR: 0.98; 95% CI: 0.96-1.00).[38]

In a study by Pinto et al.[54] CF patients above the age of 10 had greater nutritional status impairment. Malnutrition was also found in 66.7% of the sample and severe depletion of body reserves in the arm muscle area and upper arm fat area (p = 0.013).[54]

Chaves et al.[45] was found in CF patients (n = 48) statistically significant association between body mass index and triceps skinfold (p = 0.001 e p = 0.03, respectively) with the degree of pulmonary involvement, while the arm muscle circumference showed only a trend (p = 0.06) for this same association. Linear regression revealed a moderate relationship between body mass index and FEV1 (r = 0,46; p = 0,00001) and between FEV1 and arm muscle circumference (r = 0.46, p = 0.0001). 60% of children and adolescents were stunted (< p5) and had moderate to severe impairment of lung function.

Treatment of cystic fibrosis

Clinical treatment should be performed in specialized CF centers, given that this represents better patient prognosis. Although there is no cure for CF, many therapeutic interventions do retard progression of the disease.[9] The use of the multidisciplinary approach model to treat the disease is based on the observation that the creation of comprehensive care centers for CF is related to the progressively better prognosis to patients.[55]

Treatment for CF patients includes antibiotic therapy, mucolytic agents, bronchodilators, anti-inflammatory agents, pancreatic enzyme replacement and ursodeoxycholic acid, nutritional support, oxygen supplementation and physiotherapy.[56]

Antibiotic therapy

Antibiotic therapy is one of the factors that have contributed to survival rates. The antibiotic regimens used vary widely, but some principles should be followed such as: performing microbiological diagnosis and avoiding monotherapy for treatment of P. aeruginosa infection, in order to avoid resistance. Antibiotics commonly used to combat staph are the cephalosporins of first and second generation such as amoxicillin-clavulanate, macrolides,trimethoprim-sulfamethoxazole, oxacillin, vancomycin, teicoplanin and linezolid. The last three should be reserved for strains of staphylococci resistant to methicillin. For infection by P.aeruginosa, the antibiotic of choice for oral use is ciprofloxacin; with which there is already considerable experience in CF children with comparable efficacy to the parenteral use of antibiotics. Repeated use can cause resistance that is usually transitional.[9-57]

For intravenous treatment of P.aeruginosa infection, it is recommended to use a combination of an aminoglycoside (amikacin or tobramycin) with a cephalosporin, 3th and 4th generations or piperacillin/ticarcillin or piperacillin-tazobactam or carbapenems (imipenem, meropenem). Cefotaxime and ceftriaxone should not be used; even if there is in vitro sensitivity, since it does not show good anti-P. aeruginosa action. The association most frequently used in our midst is amikacin with ceftazidime.[9-57]

Inhaled antibiotics are very important in the treatment of pulmonary infection because the local deposition is high; with low absorption and systemic toxicity. Tobramycin, gentamicin, and amikacin are used most as suppressive therapy of chronic infection by P. aeruginosa and treatment of initial infection by P. aeruginosa.[57]

Studies with azithromycin have shown that use in patients with CF and chronic colonization by P. aeruginosa can lead to stabilized lung disease, reduced exacerbations and nutritional improvement. The suppression of secretion and synthesis of inflammatory mediators, alteration in neutrophil function, inhibition of alginate synthesis, protease and elastase by P. aeruginosa and reduction of their grip in the epithelium cells, are some of the possible mechanisms which cause macrolides to have a beneficial effect on these patients.[9]

Mucolytics and bronchodilators

Good fluidity of secretions is very important, since they are very thick. Besides adequate hydration, the use of a humidifier/nebulizer is recommended with simple saline or with bronchodilators, when indicated (presence of wheezing or significant spirometric response to bronchodilators.[58]

Nebulization of the hypertonic saline solution increases ciliary transport, improves the rheological properties of the sputum, and improves the hydration of the surface of the airways.[8] Elkins et al.[58] demonstrated a significant improvement in lung function and no worsening of the bacterial infection or the inflammation. Therefore, in CF patients, nebulization of hypertonic saline solution, preceded by bronchodilator inhalation, is a safe, affordable treatment, providing therapeutic benefits.

Recombinant human deoxyribonuclease (rhDNase, dornase alfa, Pulmozyme) has been shown to improve lung function, reduce sputum viscosity and the number of pulmonary exacerbations in patients with cystic fibrosis.[59]

RhDNase is s purified solution for use inhaled, which reduces the viscosity of the mucus derived from the nucleus of degenerated neutrophils. Several studies show alfadornase that is safe, effective and well tolerated in patients with mild lung disease, moderate or

grave.[60] studies report short-and long-term maximum improvement in FEV1 of about 5%-13%, depending on the severity of disease.[61] Early initiation of treatment is related the rate of improvement in function pulmonar.[62]

Inhaled bronchodilators have been used as part of the standard treatment in CF and the agents most frequently employed are the short-acting agonists. The bronchodilators can improve the respiratory function, because these patients often have bronchial hyperactivity.[8,63]

Anti-inflammatory agents

Some of the most important pathobiology in cystic fibrosis occurs not as a direct result of impaired chloride transport, but the downstream consequences of defective CFTR function, particularly the lung infection and inflammation that ultimately takes the lives of most patients. Interrupting the vicious cycle of infection and inflammation is effective in slowing the course of the disease.[64]

The pathophysiological process in CF has been the target of numerous studies. Despite such efforts, a drug that is efficient and safe for this purpose has not yet been identified.[65] Although oral corticosteroids at a dose of 1-2 mg/kg on alternate days seem to retard the progression of the pulmonary disease, the benefits are offset by the significant adverse effects, especially growth impairment. There is as yet little evidence for the use of systemic corticosteroids to treat CF exacerbations. However, systemic corticosteroids have been used as a therapeutic resource in patients with severe exacerbations, especially in the presence of bronchial hyperreactivity.[66]

Inhaled corticosteroids and high doses of ibuprofen have also been studied in CF with the objective of reducing the inflammatory process and decreasing lung injury. However the current evidence is insufficient to establish whether there is benefit in its use.[67]

Other anti-inflammatory drugs have been much less widely studied in CF like pentoxifylline, tyloxapol, gelsolin, surfactant, and hypertonic saline in varying concentrations. None of these substances should also be routinely used in the treatment of pulmonary manifestations in cystic fibrosis.[8]

Pancreatic enzyme replacement and ursodeoxycholic acid

Pancreatic enzyme replacement should be undertaken along with meals. Currently pancreatic enzymes are administered in the form of capsules containing microspheres coated with resin-resistant, thus avoiding inactivation by gastric acidity. The enzyme comes in active form in the duodenum and jejunum, allowing an increase in the absorption of fat to 85-90% of ingested substances. In patients requiring high doses of enzyme for control of steatorrhea, it is necessary to associate this with gastric acid secretion inhibitors, such as ranitidine or omeprazole to increase the intestinal pH and enhance the action of the enzyme.[8,9]

The use of ursodeoxycholic acid in high doses seems to exert a hepatoprotective effect by being a hydrophilic bile acid, increasing the transport of hydrophilic bile acids that accumulate in the cholestatic liver stimulating bile flow. Although there is no conclusive evidence regarding the use of ursodeoxycholic acid, this is recommended for patients with cholestasis-fibrosis-cirrhosis sequence. Laboratory monitoring of liver disease and its complications should be performed more often in these patients.[9,6]

Use of oxygen

People with cystic fibrosis (CF) suffer from breathing problems. Giving additional oxygen has long been a standard of care for people with chronic lung diseases. It is common for doctors to prescribe this treatment for people with CF when there is not enough oxygen in their blood.[69] Oxygen should be used if there is hypoxia, using the same criteria of indication for patients with chronic obstructive pulmonary disease.[8]

In the short term, treatment has shown some improvement in blood oxygen levels in people with CF during sleep and exercise. However, caution needs to be exercised in those with advanced lung disease where this may require further monitoring.[69]

Recent Department of Health changes to the provision of home oxygen have emphasized the importance of cost and the need for evidence of efficacy through proper assessment. The decision to start and to continue home oxygen therapy should be carefully assessed and reassessed at regular intervals.[70]

Physiotherapy

The Respiratory Therapy (FR) aims to promote improvement in the patient's respiratory mechanics, reducing your caloric expenditure, and remove the sticky mucus and exudate caused by lung infections and is the main non-pharmacological treatment.[71]

The maneuvers of airway clearance help in the removal of secretion reducing the bronchial obstruction and its consequences, such as atelectasis and hyperinflation. The main resources used in cystic fibrosis are:postural drainage, clapping, percussion, and manual and mechanics vibration, forced expiration technique, positive expiratory pressure mask, active cycle of breathing techniques, flutter, shaker, acapella and autogenic drainage.[1,71]

Chest physiotherapy (CP) is seen as a cornerstone of Cystic Fibrosis (CF) treatment. However, previous studies have suggested that adherence to CP is low. Myers & Horn investigated CP adherence and associ-

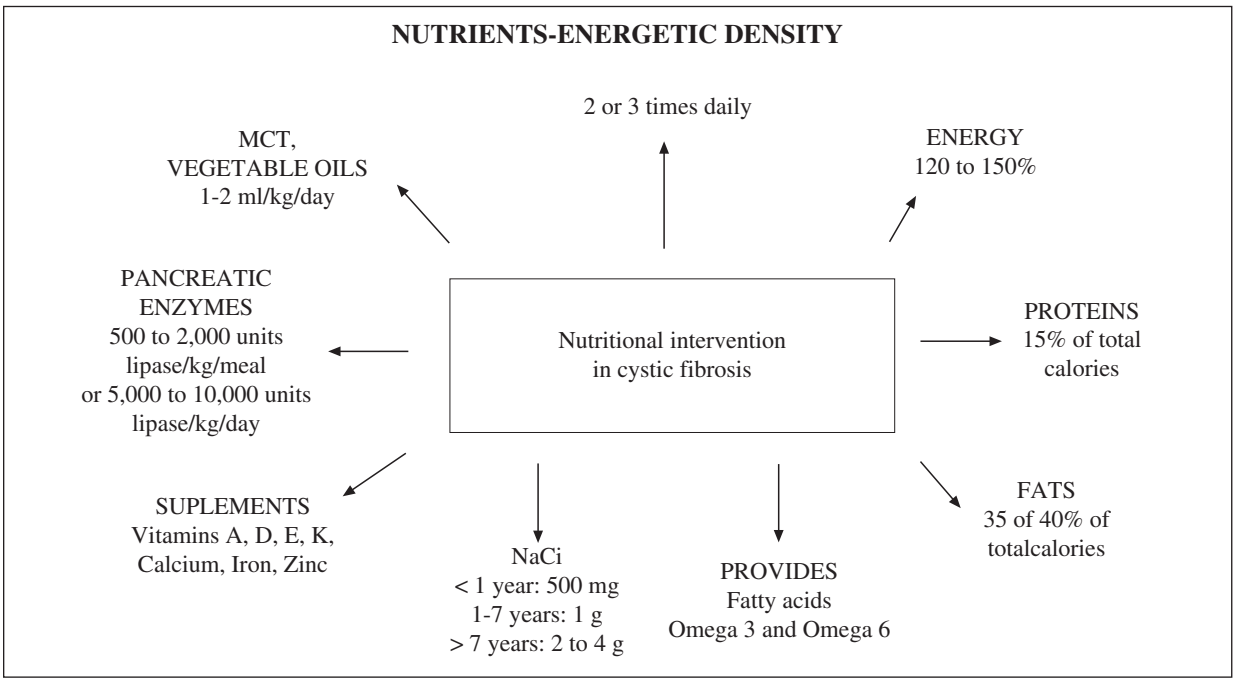

Fig. 1.—Nutritional intervention in cystyc fibrosis.

ated factors. Only 29.5 per cent reported undertaking daily CP.

Predictors of adherence included problems with fitting CP into lifestyle, a perception that CP does not help, physical consequences of CP, doing exercises instead and doing CP as and when necessary.[72,73]

Nutritional support

The importance of maintaining good nutritional status is based on a direct relationship between lung function and patient survival. Since cystic fibrosis is a chronic and multisystemic disease in constant evolution, the clinical expression of each patient should determine the energy requirements, individualizing treatment according to age and developmental stage of pathology.[42]

Due to the energy deficiency that occurs in these patients, a greater daily calorie intake is usually recommended, although it is common not to reach high caloric values in inappetent CF.[42]

Breastfeeding is not contraindicated in CF patients, but requires the careful control of steatorrhea and administration of digestive enzymes. The use of hydrolyzed milk up to two years of age is widespread, based on the need to reduce ingested enzymes.[74]

The use of energy supplements may be recommended, but it is important to ensure that they are not being used to substitute meals. There are several nutritional supplements available whose prolonged use allows an effective nutritional recovery, demonstrated by significant increase in weight, growth rate and stabilization of lung disease. The choice of supplement is often determined by the energy requirement and 1-2 kcal/ml is recommended. This may be offered before or after meals or at bedtime to maintain normal appetite.[42,74]

When oral food intake is not enough to reach desired weight, supplementation may be administered enterally via nasogastric or gastrostomy, preferably during the night.[74-7] In the past, low-fat diets were recommended in an attempt to reduce steatorrhea, but nowadays high-fat hypercaloric diets are being recommended. However, care should be encouraged in order to avoid complications. Rhodes et al. conducted a study involving 334 patients pacreato-sufficient (PS) and insufficient (PI) and found in PS, when compared to the PI, higher levels of cholesterol ($p < 0.01$) and higher triglyceride concentrations, suggesting the need for further study and care in prescribing these diets.[76]

Attainment of a normal growth pattern in childhood and maintenance of adequate nutritional status in adulthood represent major goals of multidisciplinary cystic fibrosis centers. International guidelines on energy intake requirements, pancreatic enzyme-replacement therapy and fat-soluble vitamin supplementation are of utmost importance in daily practice.[2] The figure 1, summarizes the most up-to-date information on nutritional management.

Final remark

The literature shows the need for multidisciplinary care for CF to be comprehensive because the disease is multi-systemic. The multidisciplinary, neonatal screening and clinical studies dies in the clinical and

nutritional area, should be encouraged in all centers so that support is initiated early and effectively.

The studies reviewed suggest that multidisciplinary care is essential for the integration of knowledge so as to impose the permanent update of scientific information, thereby contributing to the development of intervention strategies that enhance survival and motivate the development of skills to cope with a complex therapeutic regimen that is necessary for the treatment of CF and the prevention of its complications.

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