Monaldi Arch Chest Dis
2011; 75: 3, 178-184

REVIEW

Adult cystic fibrosis care in the 21st century

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ABSTRACT: ***Adult cystic fibrosis care in the 21st century. E. Garattini, D. Bilton, G. Cremona, M. Hodson.***

Cystic fibrosis (CF) is the most common autosomal recessive inherited disease of Caucasian populations. As a result of a variety of diagnostic and therapeutic strategies there has been a dramatic increase in the life expectancy of patients with CF in the last decades and 50% of patients are now adults. This review will focus on the disease in adults and the provision of appropriate care. The complex care required to improve the survival and quality of life in the adult patients can best be provided in a dedicated adult cystic fibrosis unit. These units currently exist in many European countries, but more are needed in Italy. ***Monaldi Arch Chest Dis 2011; 75: 3, 178-184.***

Keywords: Cystic fibrosis, Survival, Adult centres.

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Introduction

Cystic fibrosis (CF) is the most common autosomal recessive inherited disease of Caucasian populations [1] caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene. Over the past decade there has been an increase in the life expectancy of patients with CF due to many causes such as improved physiotherapy, better nutrition, new antibiotics, and the use of inhaled antibiotics and pulmozyme together with specialised centre care. Sixty years ago the CF population was composed of children, while now 50% of patients are adolescents or adults [2]. It is therefore necessary not only to have paediatricians with expertise in managing children with CF but also specialists skilled in the management of the clinical problems in adults. A system of care and facilities appropriate for adult patients must also be provided. In recent years in Italy this type of organisation has been successfully applied in centres such as in Milano and Torino [3, 4]. Currently, in Italy there are 39 CF centres, but only 4 (in Milano, Torino, Verona, Napoli) have facilities dedicated to adult care.

To ensure appropriate treatment a multidisciplinary team at the CF centre is needed [5], although in many European countries there are no specialised adult CF centres and only 15 of 34 European countries have a national CF patient registry [6], which is essential for monitoring patient numbers, treatments and outcomes. Recently there has been a major initiative with EuroCareCF Workpackage 1 to improve this situation [6].

Epidemiology

In 1938, 70% of babies died within the first year of life [7]. In contrast, in the last decade, the majority of CF patients survive into adulthood. In Italy the average total number of CF patients from 1998 to 2001 was 1,742 [8] and the proportion of adult patients more than doubled between 1988 (17%) and 2000 (41%) with about 400 patients over 30 years of age [3]. This trend can also be observed in patients from Lombardy, where there has been an increase in total CF patients from 282 in 1988 to 610 in 2003, and currently it is estimated that the total number of CF patients is approximately 600 [4]. There were 141 CF adults in 2003 compared with 190 in 2009, which means a 30% increase in adult patients [4]. During the years 1988-2001 the median age at death in Italy increased from 14 to 22 years [3], reiterating the need to involve specialists of adult disease in CF care. Two national laws were enacted in 1992 and 1993 in support of this principle. In Lombardy the median age of adult CF patients changed from 32.4 years in 2005 to 36.2 years in 2009 [4]. The Italian Registry will probably resume as part of the Istituto Superiore di Sanità and is predicted to show a continued increase in survival.

In the UK the number of CF patients aged 16 years and over increased from 50.1% in 2002 to 56.2% in 2008 [9]. Over the same period, the age at death had also risen from 23 to 27 years [9]. In 2008 the median predicted survival age is estimated around 39 years with a median age of death of 27 years old [9].

The median age of death in Europe varies from 9.5 to 27 years and the percentage of patients

over 16 to 18 years from approximately 17% to 56% [6].

In the United States in 1985 the median age of survival was age 27 while in 2009 it was 36 years [10]. In 2009 more than 47% of people with CF were adults, compared to 30% in 1990 [10].

The clinical challenge

CF is a complex multiorgan disease with a wide range of clinical presentation and severity which presents in early childhood usually with respiratory tract infections and/or intestinal malabsorption. A small number of patients are not diagnosed until adult life, usually those with mild disease.

Lung

Lung disease occurs as a consequence of chronic infection of the airways [11]. The main microrganism in adults is *Pseudomonas aeruginosa* [12] which causes a greater decline in lung function and thus is the leading cause of morbidity [13]. In the CF airway the initial infecting organisms are usually *Staphylococcus aureus* and *Haemophilus influenzae* which are usually treated with oral long-term antibiotics [14], while typical microrganisms in adults include *P. aeruginosa, S. aureus, Stenotrophomonas maltophilia, Burkholderia cepacia complex* and *Aspergillus fumigatus*. *Aspergillus* can be associated with allergic bronchopulmonary aspergillosis (ABPA) but in some patients appears to act as an infecting organism [15].

The treatment of chronic *P. aeruginosa* infection is based on chronic suppressive antibiotic therapy such as nebulised colistin or tobramycin which stabilise the patient's condition, slowing the decline or improving of respiratory function [16] and reducing IV antibiotic replacements such as dornase alfa and nebulised hypertonic saline are used to promote sputum clearance and also improve lung function and reduce exacerbations [17]. These therapies must be combined with daily airway clearance techniques taught and reviewed by an expert physiotherapist.

Lung function for pulmonary treatments represents an important outcome measure. The aim of treatment is to keep FEV_1 as close to normal as possible. In the United States the mean FEV_1 of CF patients is estimated as 76,3% in 2009 [13], 73,2% in UK in 2008 [9], approximately 73,1% in Italy in 2007 [18] and 83,8% in Lombardy in 2009 [4].

Complications

Exacerbations of infection, pneumothorax, haemoptysis, ABPA and respiratory failure are common complications of CF disease. Pneumothorax is often recurrent and it is associated with a poor prognosis [19]. It may be treated conservatively in presence of small pneumothorax (<2 cm) or with hospitalisation and intercostal tube for large pneumothoraces (≥2 cm). The average annual incidence of pneumothorax is 0.64% [20] and approximately 3.4% of individuals with CF will experience a pneumothorax during their lifetime [20].

When haemoptysis occurs, the bleeding may be scant (<5 mL), moderate (5-240 mL) or massive (>240 mL/24h), the latter treated with bronchial artery embolization [21]. Approximately 4.1% of all patients with CF will suffer massive, potentially fatal haemoptysis during their lifetime and the average annual incidence is 0.87% [22].

As the disease progresses, the patients becomes more hypoxic, a few develop cor pulmonale requiring long term oxygen therapy, others who are in chronic respiratory failure become dependent on non-invasive positive pressure ventilation [23]. When the end-stage of the disease is reached, the patients should be given the opportunity to be assessed for pulmonary transplantation.

Gastrointestinal tract

The majority of CF patients (approximately 89%) have pancreatic insufficiency [10] resulting from destruction of pancreas exocrine tissue. Therapy is based on the oral replacement of pancreatic enzymes. Adults with CF and previous pancreatic sufficiency require monitoring to pick up development of insufficiency, distal intestinal obstruction syndrome (DIOS) and constipation later in life, which are the common CF gastrointestinal complications. DIOS requires conservative treatment with oral osmotic agents (eg. polyethylene glycol), or gastrografin, or intestinal lavage with balanced osmotic electrolyte solution and rehydration [24]. Some patients need colonoscopy [25] and a few may require surgery if intussusception occurs [26].

Nutrition

Long-term nutritional management is as integral a part of modern care as pulmonary therapy and is intimately linked to pulmonary outcomes [27]. Dietetic management is based on the replacement of pancreatic enzymes and fat soluble vitamins (A, D, E, K), together with a high protein diet and high calorie intake (120-125% of the normal recommended daily allowance) [28]. The recommended Body Mass Index for CF patients is ≥22Kg/m^2 for females and ≥23Kg/m^2 for males [29]. Overnight enteral nutrition via nasogastric tube or gastrostomy provides supplementary nutritional support when BMI is suboptimal.

Liver

Since 1938 [30] liver disease has been a recognised complication of CF. In the United States 10.8% of patients with CF develop hepatic disease and 15% progress to liver failure needing liver transplantation [10]. In Europe the presence of liver disease is approximately 5% with evidence of cirrhosis and hypertension/hypersplenism in 1.16% [31].

The majority of patients present with liver disease in childhood with hepatomegaly or splenomegaly, although it may occur without any symptoms. The

Annual Assessment should include biochemical liver function tests, complete blood count [31, 32] and liver ultrasound [33]. Management of chronic hepatobiliary disease includes early treatment with ursodeoxycholic acid (UDCA) with correction of malnutrition, specific treatment of portal hypertension and liver failure, and liver transplantation [32]. It is rare for CF liver disease to develop de novo in adults.

Biliary

Asymptomatic cholelithiasis is common in CF adults [34]. Treatment of symptomatic gallstones is with laparoscopic or surgical cholecystectomy [31], depending on lung function.

Diabetes

Cystic fibrosis related diabetes (CFRD) is a common complication of cystic fibrosis [35] which increases with age and occurs only in patients with exocrine pancreatic dysfunction [36]. In the United States 22% of patients with CF develop diabetes mellitus [10], while in Europe the presence of CFRD is estimated around 11% [18]. CFRD is a distinct clinical entity caused by insulin deficiency which differs from diabetes type 1 and type 2. CFRD is present in 40-50% of CF adults and the incidence and prevalence are higher in female subjects aged 30-39 years but without sex differences [37]. CFRD is also characterised by weight loss and declining lung function [38]; furthermore diabetes has an adverse effect on CF survival. Infectious exacerbations, systemic steroid treatment and pregnancy are all factors associated with increased insulin demand [39].

The oral glucose tolerance test (OGTT) is the gold standard for the diagnosis and screening test for CFRD [40] and it should be performed annually by age 10 years in all CF patients using a 2-h 75-g OGTT. A positive test is confirmed by presence of glucose level >200 mg/dL (11.1 mmol/L) or two more diagnostic criteria for diabetes [40]. Insulin is the treatment for CFRD [41], and the dose can be adjusted depending on food intake and not by calorie restriction. Patients with CFRD can also develop metabolic and vascular complications. It is crucial that an adult CF centre has expertise in CF related diabetes management.

Bone disease

A low Bone Mineral Density (BMD) may appear around puberty [42] caused by several factors including malnutrition, vitamin D and vitamin K insufficiency, calcium deficiency, reduced levels of weight-bearing activity, glucocorticoid use, delayed puberty, hypogonadism, CF-related liver disease, CFRD and the systemic inflammatory response to pulmonary infection [43].

Low BMD was first described in patients with CF in 1979 [44] and it affects approximately 10% of CF patients [10]. A severe consequence of BMD can be rib or vertebral bone fractures which interfere with chest physiotherapy and are associated with increased morbidity and mortality. Preventive strategies include annual measurement of calcium and vitamin D levels, high milk diet, weight bearing exercise and treatment with biphosphonate [32, 45].

Vasculitis

Vasculitis is an unusual complication of CF with an estimate frequency about of 2-3% [46]. It is probably caused by antigens from bacteria or antibiotics [47] and pancreatic enzyme supplementation, which lead to deposition of immune complexes in the vascular wall [47]. The majority of CF vasculitis occurs in the presence of CF lung disease [48] and they are clinically characterised by purpura, urticarial vasculitis and bullae [49, 50] especially located on the lower extremities [49].

CF associated vasculitis may resolve spontaneously or may need oral steroid, with or without azathioprine [50]. Patients have been successfully treated with methotrexate [51] and more recently with chloroquine as an adjunct in steroid resistant cases [52].

Arthropathies

Symptoms related to the joints occur in up to 12% of CF patients [53, 54] and more commonly affect adults in the second decade of life. It was thought that there was no relationship between the severity of pulmonary disease and the occurrence of arthritis [53] until a recent study suggested an association with infection with P. aeruginosa and A. fumigatus [54]. The most common arthropathies are episodic arthritis (EA) and hypertrophic pulmonary arthropathy (HPOA). EA may affect large or small joints and the treatment is generally symptomatic with anti-inflammatory agents although steroids may be necessary, while HPOA is characterized by clubbing and chronic periostitis of the long bones with or without periosteal new bone formation and usually occurs in the lower limbs. The treatment is based on non-steroidal anti-inflammatory agents for pain and occasionally corticosteroids, while pamidronate can be useful in severe or refractory cases [55].

Sinusitis and nasal polyposis

CF patients can be affected by paranasal sinuses due to the presence of CFTR in the upper airway [56]. Up to half of the patients suffer from chronic rhinosinusitis (RS) [56, 57] and another third report intermittent RS symptoms. About 24% of CF patients with nasal polyps require surgery [10], while others respond to inhaled steroids.

Predominant clinical signs of RS are chronic nasal congestion, rhinorrhoea, mouth breathing, anosmia, facial pain and sleep disorders [58]. Physical examination, including nasal endoscopy, should be used for diagnosis [59]. The most common bacteria isolated from the sinuses of CF patients vary with age: *P. aeruginosa* appears to be

more significant in older patients, while *S. aureus* and *H. influenzae* are found predominately in younger patients [60].

Reproduction

With the improvement of survival of people with CF and rapid growth of the adolescent and adult population, education and counselling for sexual health related issues have been included in the daily routine of CF care [61].

Men

Men with CF are azoospermic due to maldevelopment of the vas deferens, epididymis and seminal vescicles. Infertility is thought to occur in at least 98% of men with CF [62]. Recently, the management of male infertility has been transformed with the introduction of sperm aspiration from the epididymis and intracytoplasmic injection into ovules obtained from the female. The eggs are fertilised and returned to the uterus [63]. Thus adult CF clinics should have strong links with male infertility services.

Females and Pregnancy

Successful pregnancy is increasingly common in adult CF females [64]. It requires careful planning to ensure good outcomes. Planning should include discussion of: a) partner carrier status; b) careful evaluation of current therapies to avoid foetal abnormalities; c) assessment of pulmonary function and nutritional status.

While pregnancy is more difficult in those with an FEV_1 less than 50% predicted [32], it is well tolerated by women in good health maintaining adequate nutrition, with good outcomes for mother and baby. Some of the mothers develop gestational diabetes [65].

Psychological

CF is diagnosed either at birth or in the first few years of life which generally results in CF patients to develop a considerable understanding of their disease [66]. For this reason psychological support is an essential part of CF care [67].

Transition may have a negative psychological impact in CF patients, but when planned and started early with the adolescent, their family and the healthcare team, it can be a positive experience [68]. Furthermore young adults with CF are known to indulge in risky behaviour and require counselling regarding alcohol, tobacco and recreational drugs.

Transplantation and terminal care

CF is a disorder that leads to respiratory failure and premature death. Pulmonary transplantation is an important therapy for end-stage CF lung disease. Survival once patients reach an FEV_1 of 30% was only 2 years in 1989 [69], but improved to 5.3 years in 2003 mainly due to the impact of lung transplantation [70]. The adult CF physician must be skilled in recognising end-stage disease and timing discussion and referral for transplantation appropriately. As there are not enough lung donors for all CF patients requiring transplantation, in this stage of the disease palliative care is an approach that may improve the quality of life of patients and their families [71].

Specific discussions around the appropriateness of investigations, the discontinuation of acute treatment and the continuation or cessation of assisted ventilation are also necessary. As death approaches treatment should focus on symptom control; generally the nurse specialist, together with the patient and family, should assess and formulate an appropriate plan of care, including the opportunity to choose home or hospital as the place to die [72].

Spiritual

People with end-stage cystic fibrosis live with the knowledge of imminent death and a chaplain/spiritual advisor can help them discuss their anxieties [73].

Travel

The increased life expectancy over the past three decades enable people with CF to participate in every aspect of modern life. There are no European recommendations on issues specifically related to travel [74]. The main predictors of medical safety during air travel are the duration of flight and patients' condition [74]. A recent study [75] has demonstrated that spirometric results, e.g. FEV_1, may be more relevant than pre-flight SaO_2 or PaO_2 as a predictor of in-flight oxygenation. Patients may need a "fitness to fly" test to decide whether they will require in-flight oxygen. It is important that patients have a health insurance which does not exclude pre-existing conditions. They should carry a letter describing their condition and current medications. They should be advised to keep well hydrated and take extra salt in hot climates. Sunburn should be avoided. There is a particular risk in travelling to remote areas such as tropical Southeast Asia and Northern Australia because of the high frequency of Burkholderia pseudomallei which is known to cause severe pneumonias in CF patients [76].

Economic issues

The increased survival of people with CF has led to a larger number of CF patients seeking higher education, vocational training and employment. Some patients are not able to work requiring assistance from their family: in this case advice may be required regarding any state benefits.

Staff

Cystic fibrosis is a complex disease requiring an holistic approach to treatment [77]. The complications in adult CF discussed in this article demon-

strate the need for a highly skilled core team consisting of an adult CF physician, clinical nurse specialist, physiotherapist, dietician, social worker, psychologist, pharmacist, occupational therapist, clerk, secretary, data manager, gastroenterologist, diabetologist, ear nose and throat specialist, rheumatologist, obstetrician/gynaecologist/fertility specialist, thoracic surgeon and transplant team [78].

Facilities

The CF centre needs to arrange appropriate inpatient and out-patient care, including annual assessments and home treatment [32,78]. Both inpatients and those receiving intravenous antibiotic therapy at home should be discussed at least once weekly in a multidisciplinary meeting with all the members of the CF team [32].

Inpatients

A CF specialist centre must have sufficient beds available at all times to allow immediate admission for patients with recurrent exacerbations. The beds should be in single rooms with en-suite bathrooms or separate toilet and bathroom facilities, in order to reduce cross-infection. In addition, hand washing facilities and alcohol-based hand rubs must be present in each patient cubicle.

Outpatients

Patients should be seen in clinic generally every 3 months or more often in case of severe disease. Every visit should include a routine history and physical examination, measurement of weight, pulse oximetry, pulmonary function tests and sputum or cough swab cultures. It is important that patients are seen in separate rooms to reduce cross infections.

Home care

As repeated periods of hospitalisation are disruptive to school, work and family, home care is usually favoured by the patients. Sometimes intravenous antibiotic therapy is given in hospital for a few days to be continued at home. The CF Nurse Specialist has a central role for an effective home treatment service that ensures that the home conditions are appropriate for giving intravenous treatment.

Annual review

Once a year patients attend a specialist CF centre for an annual review which includes more detailed assessment of the patient's conditions. Full history and examination, lung function tests and blood gases should be determined as well as a chest x-ray, bone mineral density scan, OGTT and full haematological and biochemical tests.

Costs

It is recognised that Cystic Fibrosis care is costly but investment in high quality CF centres yields good outcomes [79]. A mechanism to ensure equitable provision of high cost CF specialist drugs is preferred.

Conclusion

In the last sixty years CF has moved from a little known genetic condition, usually fatal in infancy and early childhood, to a complex multisystem disorder now affecting as many adults as children. Despite modern therapies, the median age of death remains in the late twenties hence the CF community continues to look for new treatments that will further improve life expectancy.

This paper has outlined the detailed care needed by adult CF patients. Soon more than 50% of patients in Italy will be adults, and it is not appropriate to share rooms and clinics with children. Severe respiratory complications, respiratory failure, life threatening, haemoptysis and pneumothorax occur mainly in adults. Osteoporosis and diabetes are much more common in adults. There are also unique problems to adults such as pregnancy and male infertility. The risks of alcohol, smoking and recreational drugs are seen mainly in adults. In addition, adult CF are more likely to need percutaneous endoscopic gastrostomy, portacaths, oxygen, non-invasive ventilation and transplant assessment than children. Adult CF physicians gain expertise in all these areas and specialised adult CF clinics are essential. Following the creation of the first adult centre in the UK in 1965 there is now a network of adult centres in the UK and other European countries. It is now time that such care is provided for all adult patients in Italy.

Acknowledgements: The authors thank Prof. Carla Colombo of the Ospedale Maggiore Policlinico in Milano for the data regarding CF patients in Italy and Vivisol srl who financed EG's stay at the adult Cystic Fibrosis Unit of the Royal Brompton Hospital in London UK and so made this report possible.

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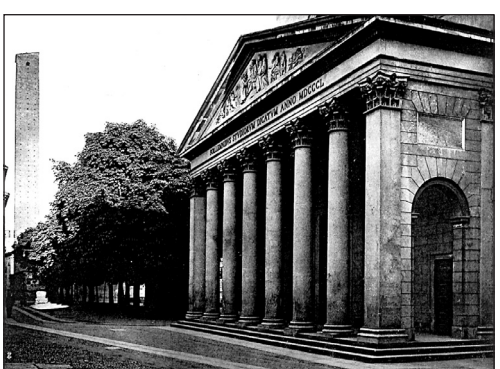

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