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Standards of care for patients with cystic fibrosis: a European consensus

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1. Introduction

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1,2]. This results in dysfunction of the apical membrane CFTR protein which regulates chloride and sodium transport in secretory epithelial cells [1], with abnormal ion concentrations across the apical membranes of these cells. The clinical consequences include multi-system disease characterised by progressive pulmonary damage leading to respiratory failure, pancreatic dysfunction, liver disease that may progress to cirrhosis, gut motility problems, and elevated sweat electrolytes. Virtually all men with CF are infertile due to atresia or complete absence of the vas deferens.

Cystic fibrosis is a complex disease requiring a holistic approach to treatment [3]. Center care by a team of trained and experienced health professionals is essential for optimal patient management and outcome [4]. Specialist care in dedicated CF centers is associated with improved survival and quality of life [4,5]. Such care involves frequent clinical evaluations and monitoring for complications, by physicians and other healthcare workers specifically trained in the management of CF and early treatment interventions.

Standards of care define the optimal service provision necessary to deliver the best outcomes possible for patients. Several guidelines have been written to assist CF caregivers in the evaluation and monitoring of patients, detection of complications and prevention of clinical deterioration [6–9]. However there is lack of uniformity in many of the agreed European recommendations e.g.; the necessary infrastructure for a CF center; the minimum standards for routine evaluation and assessment of patients; the documentation of results in a standard database and; the management of complications. We are convinced that intensive treatments, both prophylactic and as a response to acute events, decrease morbidity and increase survival and quality of life.

The aim of this consensus document is to define standards for the routine evaluation, monitoring and treatment of patients with CF in Europe. We hope that these will be adopted by all European CF centers to provide a quality assurance instrument and a basis for audit of CF care.

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Assessment of centers against these standards will also provide important insights into current practice in a large number of European patients and provide comparative data from different centers.

2. Definition of a center

The CF center should have the staff and facilities to provide comprehensive care and be capable of treating all CF associated complications. The center should be an integral part of a university or teaching hospital with funding guaranteed by the provider of medical care. In countries where there is shared care between the CF center and smaller hospitals which are closer to the patient's home the center should coordinate care and hold ultimate responsibility for the patient's treatment and outcome. Shared care cannot be guaranteed to be equivalent to center care and should be reserved for patients who live far from a CF center or for whom social difficulties make regular attendance at the center impossible. Shared care clinics must meet the same standards as at the main center, allowing that this may require help from the multidisciplinary center team and subspecialty consultations from the center.

A center should normally care for a minimum of 50 patients. The center director should be an experienced CF physician working in close collaboration with at least one other physician knowledgeable in CF medicine. In addition, CF centers should have varied numbers of specialist CF nurses, dietitians, physiotherapists, social workers, psychologists, pharmacists and microbiologists according to patient numbers. Also the CF center should have close links with consultants within the hospital or at hospitals nearby specializing in gastroenterology, hepatology, endocrinology, ear, nose and throat (ENT) surgery, general, hepatobilary and pediatric surgery, radiology, obstetrics and gynecology (including experts in assisted conception), infectious diseases and infection control, rheumatology, ophthalmology and nephrology. There should be effective referral and assessment protocols with a national transplant center.

The center should have the following facilities available: a radiology department with CT scanning facilities; expertise in bronchial artery embolization for pulmonary hemorrhage; a pulmonary function laboratory; expertise in the placement of totally implantable venous access devices, nasogastric and gastrostomy tubes; a microbiology service expert in examining specimens from people with CF with established contacts with a CF microbiology reference laboratory; a full diagnostic capability including reliable sweat testing and CFTR gene mutation analysis.

There should be written guidelines and facilities for the treatment of all complications of CF such as: pneumothorax, hemoptysis, allergic bronchopulmonary aspergillosis (ABPA), mycobacterial infection, distal intestinal obstruction syndrome (DIOS), gastrointestinal bleeding, portal hypertension, cirrhosis, diabetes mellitus, osteoporosis, respiratory failure, cardiac failure, pancreatitis, hearing loss, nasal polyposis, chronic sinusitis and other ENT complications.

Patients should have 24-h access to the CF center for telephone advice or for emergencies or other consultations.

3. Members of the multidisciplinary team

It is essential to provide multidisciplinary care for patients with CF. The CF team members should be an integral part of the multidisciplinary CF care team. Team members should be registered by the State/Countries Health Authorities and recognized as fit to practice within that country. Each of the members would be responsible for developing their own professional practice within the context of the multidisciplinary team, ensuring that they keep up to date with new advances and developments in treatment and enhancing their own research-based practice. The CF team members have a responsibility to maintain and increase their specialist knowledge by attendance at relevant postgraduate courses, lectures, national and international conferences and by membership of their national and/or European CF groups. They should act as a resource for the training, education, development and support of others involved in CF care including their colleagues at the CF center and those working at hospitals providing shared care. These activities should be targeted at improving the quality of patient care.

3.1. The CF center director

The multidisciplinary team should be led by the center director. Because respiratory disease accounts for most of the patients' morbidity and mortality, the center director should have specialist training in pediatric or adult respiratory medicine. The complex nature of CF care demands that the director's major professional commitment should be treating people with CF and management of the center. Center directors will spend a substantial part of their working week involved in CF care.

3.1.1. The center director's role

- Be an advocate for every patient.
- Be up to date with evidence-based optimal CF treatment practices and ongoing international research initiatives.
- Lead the multidisciplinary team and participate in regular weekly staff meetings to review patients' health status and discuss any other matters relating to the running of the CF center.
- Audit the center's performance and practices, and participate in a national database.
- Ensuring that the center's outcome is being monitored and appropriate process changes are instituted as needed.
- Establish a network of expertise within the center hospital or nearby hospitals for non-pulmonary CF

associated problems, e.g. in obstetrics and gynecology, fertility issues, rheumatology, gastroenterology etc. as described above.
- Secure from the hospital management adequate outpatient and ward facilities in which to provide care for patients attending the center and plan for future care needs.
- Ensure reliable communication with all patients and families, including older patients, and use feedback on the service provided by the center.
- Initiate research with local colleagues and be the link person for contribution to multi-center national and international studies.
- Develop a local education program: training future CF clinicians, ensuring that the CF team members remain up to date by attending national and international meetings, formally update shared care centers.

3.2. The CF specialist

The CF center director should work with at least one consultant colleague who can share clinical responsibility, provide continuity of expertise when the director is absent, and collaborate in CF related research. He/she should have a major interest in pulmonology or gastroenterology and have received accredited training in CF medicine. The CF specialist should devote a minimum of one third of his/her time to the CF center. The CF specialist should be up to date with evidence-based optimal treatment practices and ongoing international research initiatives.

3.3. The CF specialist nurse

The CF specialist nurses have responsibilities to patients, families, and to the staff involved in patient care. They should be committed to the care of patients with CF and devote all, or almost all, of their time to the center.

3.3.1. The CF specialist nurses responsibilities:

- Advocacy for every patient
- Be up to date with current treatment practices
- Maintaining and teaching clinical skills and practice
- Professional development
- Support and advice
- Education and research,
- Patient and family liaisons

The proportion of time devoted to each of these roles and the training required to achieve them may differ between countries and centers. The specialist nurse role should develop to meet the needs of the local CF population.

Specialist CF nurses should be involved at certain key times in the patient's and family's life; at diagnosis, in planning the transition from pediatric to adult care, from the first discussion about lung transplant, and in terminal care. They should be involved in providing support and information about fertility and pregnancy and in following a secondary diagnosis (e.g. CF related diabetes).

Cystic fibrosis is a demanding disease to manage for both the patient and the CF Team. Patient and family advocacy is one of the most important roles for the specialist nurse. Patient well being and satisfaction are a particular focus in nursing care and successful advocacy will help achieve this.

Specialist nurses are actively involved in making decisions about treatment and monitoring care. In addition to the practical support they provide with intravenous therapy and enteral tube feeding, they have a responsibility to ensure that every patient receives optimum care for their individual needs. Specialist nurses coordinate care between patient and family, community services and hospital, both practically and through support and advice. This is achieved through their role as an educator, a consistent caregiver, a counselor and a confidant [10].

3.4. The CF center physiotherapist

The CF physiotherapist should be involved in the evaluation of patients, providing advice on airways clearance techniques, quality control, and professional development [11]. In cooperation with the patient and family they should develop an individualized, reasonable, optimal, effective and efficient physiotherapy regimen. This should take into account all relevant physical and psychosocial factors. Modern physiotherapy in CF is primarily preventative and has to be incorporated into each patient's daily routine [12]. Therefore physiotherapy must always be carried out in a way that makes future cooperation possible and encourages adherence.

The CF center physiotherapist should assess patients every 1–3 months or at every outpatient clinic visit by: 1) carrying out and interpreting the results of pulmonary function tests and respiratory symptoms and signs and exercise capacity; 2) monitoring sputum volume and characteristics, and the degree of dyspnea; 3) assessing posture, chest mobility, muscle strength and endurance; 4) evaluating treatment quality and adherence. A full treatment session and an assessment of physical capacity by standard protocols should be carried out as part of the Annual Review. Full treatments may also be given at the clinic or during home visits. Each individual's physiotherapy program needs to be continuously modified as age, needs and circumstances change. This may help maximize adherence.

3.4.1. The CF center physiotherapist has an important role in:

1. Inhalation therapy:
   a. choice of appropriate inhalation device(s)
   b. training of the patient/family in its optimal use

   c. handling, cleaning and need for servicing and replacement of the device
2. Airway clearance therapy:
   a. choice of technique(s)
   b. training of the patient and carers in its optimal use.
3. Physical education and exercise
   a. providing the patient and family with appropriate and stimulating physical education and exercise programs.
4. Education:
   a. improving and up-dating patients', families' and locally involved physiotherapists' knowledge of CF and its treatment.

3.5. The CF dietitian/nutritionist

The CF center dietitians'/nutritionists' responsibilities are to advise and educate patients and care givers about the principles of nutritional management in CF. This will include some or all of the following: nutritional requirements and provision of nutritional requirements at varying stages of health and disease, pancreatic enzyme replacement therapy, vitamin therapy, assessment of nutritional status and CF related diabetes. Age specific individualized advice, nutritional intervention and nutritional care plans to suit the patients' needs and their nutritional and clinical status should be developed. Advice should be appropriately timed and supported by appropriate literature and aids. This is an ongoing and evolving process and with increasing age it is the role of the dietitian to ensure self-knowledge and self-care are developed.

The same dietitian should provide both inpatient and outpatient advice to ensure continuity of care or excellent routes of communication are required to prevent the minutiae of care being overlooked.

Clinical dietetic practice should be evidence-based, reflect current research, clinical guidelines and consensus views. The specialist CF dietitian should participate in multi-professional audit and research and be a resource on nutrition for the training, education, development and support of others involved in CF care. The CF center dietitian should play an active role in nutritional surveillance and patients should be assessed on a regular basis with all aspects of nutrition and gastrointestinal status being reviewed [13,14]. The frequency and type of assessment will vary with age.

A formal dietary assessment combining a recorded diet diary and dietetic interview should be undertaken at least annually. This should incorporate: a review of nutritional intake, enzyme intake including dose, timing and method of administration and knowledge of adjustment of dose to fat content of meals and snacks, bowel habit, stool frequency, symptoms/episodes of distal intestinal obstruction syndrome and constipation, adjunctive therapies, vitamin supplements, mineral supplements, oral and enteral supplemental formulae, herbal and alternative therapies, review of diabetic treatment or glycaemic status, presence or absence of liver disease, changes in nutritional status over time, body image and patterns of disordered eating, and osteoporosis and its treatment. In adult women it is also an opportunity to raise awareness of the need for preconceptional nutritional counseling [15].

Anthropometric measurements: At each clinic visit accurate measurements of weight (in kilograms) and length or height (in meters) and head circumference (in centimeters) in young infants, should be made. These values should be charted to allow for sequential assessment of growth and changes in nutritional status and to allow comparison with reference values [16]. Values should be expressed either as percentiles, as percentage of the normal values for age or as standard deviation (S.D.) or Z scores. Percentage weight for height, weight for age and height for age are often used when expressing the nutritional status of children though their reliability has been questioned [17]. BMI percentile charts should also be used for children to give a more accurate interpretation of nutritional status especially in the stunted individual. As some patients may develop kyphosis, maximum attained height should be used in the calculation of BMI. BMI should be calculated at each clinic visit to allow for sequential assessment of nutritional status.

Assessment of pancreatic status and intestinal absorption: In pancreatic insufficient (PI) patients some measure of the adequacy of intestinal absorption should be undertaken annually or more frequently if clinically indicated. Plasma levels of the fat-soluble vitamins A, D and E should be measured annually and an assessment of vitamin K status made by measuring the prothrombin time. The appropriateness of enzyme therapy should also be assessed. This will include knowledge of enzyme use including dose, timing, method of administration and enzyme titration to the fat content of the meal or snack [18,19]. In pancreatic sufficient (PS) patients who carry CF genotypes known to be associated with pancreatic insufficiency [20] annual assessment of pancreatic function should be undertaken using fecal pancreatic elastase 1 [18,19]. In patients carrying genotypes known to be associated with prolonged preservation of pancreatic function, the assessment can be less often.

Pubertal development may be delayed in patients with cystic fibrosis [15]. A standardized method of assessment of pubertal stage should be performed annually from 10 years of age. Estimation of skeletal age should form part of the assessment of any child with stunting or pubertal delay.

Bone mineral density and body composition should be assessed by dual energy X-ray absorptiometry (DEXA) scans. These should be considered as part of the nutritional assessment in all CF patients over 10 years of age [16]. There is currently no consensus on the appropriate interval between DEXA scans but sequential data is likely to prove helpful in planning future care and in determining a future consensus position.

3.6. The CF social worker

Social workers provide expertise in helping with patients' and families' emotional and practical needs, especially when extra support is needed at difficult times e.g. at diagnosis, when health is deteriorating, when there are relationship issues, and around transplant and death. The CF social worker must have an understanding of how the disease affects the lives of patients and their families on a day-to-day basis and long term. They should bridge the gap between hospital and home life, visiting patients at home when possible, and liaising with locally available support so that local services can be accessed. They are able to contribute to the multidisciplinary CF team to help build up a holistic understanding of the patient's life. This may include family dynamics, educational and career issues, relationships and other psychosocial issues. Social workers can help families cope more effectively by assessing their practical needs and then providing a range of services to meet them. They possess a working knowledge of the complex system of benefits and allowances and are able to provide advocacy for patients and liaison with other agencies. Vital empathic support is provided for relationship difficulties and in alleviating perceptions of increasing isolation as health deteriorates. Patients of any age with CF and those close to them are likely to be vulnerable to psychological stress and seemingly insurmountable social problems. The social worker has an expertise that complements that of the clinical psychologist. Together they are able to work closely with the patient and family or partner to resolve, or at least minimize, these issues.

CF social workers should have a minimum of 3 years working experience after qualification since they need to have the confidence to make professional decisions. It is also important that they have experience in both child and adult protection work and can bring this knowledge to the multidisciplinary team. The social worker should have a good understanding of the social, as opposed to, the medical model so that the clinical service is balanced and holistic. Case recording should adhere to each country's statutory guidelines with regular summaries on each case file. Standard assessment forms should be used to detail individual patient's needs and help in drawing up a care plan.

The social workers' professional development should include training about any new legislation affecting their role and continuing education about CF issues.

3.7. The CF psychologist

People with CF and their relatives are vulnerable to a range of psychological difficulties [21]. The nature of the condition and its treatment impact on children's, adolescents' and adults' abilities to respond to ordinary developmental tasks and extraordinary life events. As the condition progresses, physical deterioration can further impact on psychological well being and quality of life (QoL). In order for the psychologist's role to be effective, it is recommended that the post should be no less than 50% of their working time.

3.7.1. Essential responsibilities

CF center psychologists must be registered with their national governing body. They must have a thorough understanding of individual psychological development of family relationships and of the developmental stages of CF. The key responsibilities to undertake are: 1) a comprehensive assessment of, and intervention in, emotional, behavioral and psychological difficulties, using evidence-based treatments where indicated and making onward referrals to other agencies when appropriate; 2) an integrated post-diagnosis and annual review assessment/screening and support, either face-to-face (preferable), and/or utilizing psychometrics (always including QoL); 3) the inclusion of all psychological work in the context of the CF Team (e.g., running parallel outpatient clinics); 4) an active participation in transition programs, to both high school and adult services; 5) an assessment of the patient's and family's psychological resources and support interventions before and after lung transplantation.

3.7.2. Desirable responsibilities

In conjunction with other professionals when appropriate psychologists should take a lead role in the management of partial adherence and consult on, and participate in, the application of evidence-based approaches i.e. cognitive-behavioral techniques to managing procedural distress [22] and feeding behavior problems [23,24]. In addition the center psychologist should address psychological factors associated with chronic pain and the effects of segregation, provide a consultation and supervision service to other CF team members, and undertake dissemination of the psychological effects of living with CF within the team.

Helping and supporting the CF team during routine care and at times of crises (e.g. when a patient deteriorates quickly and/or dies), is another important part of the psychologist's responsibilities. This may be achieved by a combination of formal and informal supervision/support groups. Other professionals may be involved, for example senior nurses or the social worker.

3.8. The CF center clinical pharmacist

The treatment of CF involves multiple medications [25]. Drug therapy regimens often include aerosolized bronchodilators and antibiotics, vitamin supplements, pancreatic enzymes, and insulin for patients with diabetes. Either in hospital or at home, intravenous antibiotics are routinely used to treat respiratory exacerbations. The clinical pharmacists should advise and monitor for potential and actual drug interactions in complex regimens.

Inhaled drugs: For most inhaled drugs, the optimal drug-inhaler combination is not known. It is the task of the clinical pharmacist to find out together with other team members (CF specialist, physiotherapists, CF specialist nurses), from existing knowledge, which drug-inhalation device combinations are most appropriate and which drugs can be safely mixed together and administered.

Intravenous antibiotics: Antibiotics with a narrow therapeutic margin, such as the aminoglycosides, are dosed both on body weight and expected renal clearance, but their dose and dosing interval need to be individually adjusted to ensure maximal therapeutic benefit and minimal toxicity. This can be achieved by measuring serum drug concentrations and by using pharmacokinetic software. It is the task of the clinical pharmacist to interpret the pharmacokinetic data and to calculate and advise on the optimal dosing regimen. In home intravenous antibiotic treatment programs care must be taken that intravenous drugs are prepared under aseptic conditions. Stability permitting, some intravenous medications can be prepared and dispensed for as long as one week by a clinical pharmacy with the appropriate utilities and experience.

Oral drugs: Patients often have to take a large number of drugs every day. The clinical pharmacist can advise on drug combinations that can reduce the number of prescriptions. Also, where enteral feeding tubes are in place the clinical pharmacist can advise on how these might be used as a route for drug administration. The clinical pharmacist should advise on drug-to-drug interactions, potential treatment side effects, drug/nutrient interactions and about alternative, less expensive therapy if available.

Patient education: Patients are responsible for taking the right doses of the prescribed medications at the right times in the right order. Patients with CF usually have very complicated drug regimens. The clinical pharmacist can help educate patients about the proper reconstitution and inhalation of drugs, and why they are best taken in a particular order.

3.9. The clinical microbiology specialist

3.9.1. Microbial pathogens in CF

Bacterial lung infections are responsible for most of the morbidity and mortality of patients with cystic fibrosis [26–29]. Respiratory viruses can also cause acute exacerbations. Some patients develop allergic bronchopulmonary aspergillosis (ABPA). Polymicrobial infections are frequent in CF lung disease. The microbiology of the infections is often different from similar infections in non-CF patients and the phenotypes of the offending bacteria are frequently atypical.

The most commonly isolated bacteria are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, the *Burkholderia cepacia* complex including several related genomovars, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Pandorea apista*, mycobacteria other than *M. tuberculosis* (MOTT). The more familiar respiratory pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*, are less common (8) but can play an important pathogenic role. Occasionally patients may be chronically colonized by Enterobacteriaceae species. *Aspergillus fumigatus* and *Candida albicans* are frequently isolated from CF sputum. The former may result in ABPA but the latter rarely if ever causes disease.

The frequent use of antibiotics in patients with CF encourages the development of antimicrobial resistance. Resistant pathogens may require susceptibility testing against unusual antibiotics and/or synergy testing. There is at present no evidence that synergy testing is clinically helpful, nor that there is any correlation between antibiotic sensitivity in vitro and clinical response [30]. The widespread use of nebulized antibiotics in CF care means that the usual breakpoints (susceptible–intermediate–resistant) are not valid and may be misleading in CF bacteriology. Furthermore, in patients suffering from chronic *P. aeruginosa* infection, the biofilm mode of growth means that the bacteria are virtually never eradicated. The therapeutic aim, therefore, is chronic bacterial suppression, a strategy not generally used in other patient groups. However, intensive and early antibiotic therapy is used in many countries and is effective in eradicating first and/or intermittent *P. aeruginosa* colonization in all age groups. Some bacterial species can cross-infect between patients in CF centers or during social activities (e.g. camps, exercise classes).

3.9.2. Laboratory issues

The complicated microbiology of patients with CF necessitates a specialized knowledge and experience which can only be gained from cooperation with large CF centers. Problems include a) not recognizing typical CF bacteria or fungi as pathogens (e.g. *B. cepacia* complex, *Aspergillus* species), b) misdiagnosis of CF bacteria due to atypical phenotypic appearance (e.g. mucoid *P. aeruginosa*), c) not investigating for mycobacteria other than *M. tuberculosis*, d) not performing extended susceptibility testing including antibiotics used infrequently in other groups of patients, e) not being able to perform typing of CF bacteria, and not cooperating with reference laboratories undertaking such typing, in order to detect problems of cross-infection, f) the frequent and repeated administration of potentially toxic antibiotics, g) failure to appreciate the different pharmacokinetics of many antibiotics in patients with CF and the need to monitor antibiotic concentrations in individual patients, h) some patients with CF are colonized or infected with *P. aeruginosa* or other Gram-negative bacteria for prolonged periods of time. The clinical distinction between colonization and infection may require measurement of specific antibodies, i) similarly the diagnosis and monitoring of ABPA requires antibody measurements.

These problems and possibilities are not widely known outside specialized CF laboratories. If a non-CF laboratory identifies an important pathogen such as *B. cepacia* complex in the context of a shared care setting, the

identification MUST be confirmed by the specialist CF microbiology laboratory.

3.9.3. Cooperation between CF clinicians and clinical microbiologists

The complicated microbiology requires the use of selective media for unusual pathogens and a specialized knowledge about a) prophylaxis, including the prevention of cross-infection, b) antibiotic therapy including combinations, synergy testing etc., c) biofilm infections and the chronicity of infections, d) the side effects of antibiotics. Such knowledge and skills can only be gained by close and long-standing cooperation between the committed clinical microbiologist and the CF center clinicians. Individual patients, prophylactic, diagnostic and therapeutic problems should be discussed on a regular basis.

4. The routines of CF care

4.1. Outpatient care

Patients should be seen every 1–3 months, preferably every month. Newly diagnosed infants or patients with severe disease should be seen more often, and those with mild phenotypes or atypical CF may be seen less often, every 3–6 months.

The outpatient visit should take place in a designated clinic in the hospital. The CF physician and nurse should see the patient and all other members of the CF team should be accessible. Other specialists may see the patient according to local arrangements. Every visit should include a routine physical examination, measurement of weight, oximetry, age appropriate pulmonary function tests and sputum or cough swab cultures. In children, height and in young children also the head circumference should be measured and recorded on percentile charts. Medication should be reviewed and any treatment changes fully discussed with the patient/family and communicated to the general practitioner. Sufficient time should be allocated for each patient.

Outpatient consultation for patients with *B. cepacia* complex or MRSA infection should be on a separate day, at the end of the day, or in a different location from the other patients. Separate clinics for patients with and without chronic *P. aeruginosa* infection should be considered and are now the rule in many CF centers.

When indicated, the center should have the ability to organize an admission or home intravenous treatment to start within the next 24–48 h. In the latter situation the initial intravenous antibiotic dose should be given under medical supervision and all aspects of home therapy should meet previously agreed criteria. Sometimes intravenous antibiotic therapy is given in hospital for a few days to be continued at home. This allows easier monitoring of early blood drug levels and possible side effects.

Patients should have 24-h access to the CF center either by telephone or direct contact for emergencies or other consultations. For routine telephone enquiries it is recommended that there is a specified time each day that patients can use to consult a specialist CF doctor or nurse.

4.2. Inpatient care

A CF specialist center must have sufficient beds available at all times to allow immediate admission. Each center should have a clear infection control policy. The beds should be in single rooms, mainly to prevent cross-infection, and preferably with private en suite toilet and bathroom. Hand washing facilities and alcohol-based hand rubs must be present in each patient cubicle. Patients with *B. cepacia* complex or MRSA infection must be nursed in individual cubicles on a separate ward. Because of the varying virulence of different *B. cepacia* complex genomovars, all *B. cepacia* complex infected patients should be separated from each other, i.e. there should be no patient interaction allowed inside the hospital and patients should be advised not to mix socially outside the hospital.

Separate rooms for each patient are also necessary in order to promote adherence to physiotherapy and facilitate the inhalation of antibiotic drugs. Concomitant review and treatment by allied health professionals (e.g. physiotherapists, dietitians, social workers etc.) should be available. Assessment of hyperglycemia and overnight oxygen saturations should be performed at each admission for an infective exacerbation. At least once a week sputum samples should be cultured and spirometry recorded. Patients should receive physiotherapy treatment, including sputum mobilization techniques, at least twice a day. Facilities for supervised physical exercise, including pulse oximetry and additional oxygen at the site of training, should be available. Clear protocols should be available for the dosing and administration of antibiotics (including measurements of antibiotic serum levels), feeding by nasogastric tube or gastrostomy, the treatment of a pneumothorax, management of hemoptysis including bronchial artery embolization, the diagnosis and treatment of ABPA and CF related diabetes.

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 and the medical and nursing team on the ward.

4.3. Shared care

The practice of the CF center sharing the care of patients with the staff at their local hospital has become established because some families and patients cannot, and others will not, travel long distances for their routine treatments.

Agreed models of shared care are needed as a response to patient\parent demand but they should not be allowed to result in suboptimal care. There is no place for doctors working in isolation and caring for small numbers of people

with CF. A satellite CF unit in close liaison with a CF center should have a minimum of twenty patients and input from a dietitian, physiotherapist, and nurse, each with a special interest in CF. Patients with CF at the satellite unit should attend CF dedicated clinics and should not be included in general pediatric or adult respiratory outpatient sessions. Basic care at the satellite unit should be of an equivalent standard to that delivered at the center. Only in exceptional circumstances should the CF center agree to share management with a doctor who cares for very few patients.

Contact with the center may be by the center team visiting the satellite unit or by the patient periodically attending the CF center or both, at least once and ideally twice a year. The center team should perform the Annual Assessment and ultimate responsibility of care should rest with the CF center director.

Shared care is more appropriate for children with CF than for adults. The latter are likely to have more complex disease requiring input from other specialists who have acquired an expertise for CF associated problems in their own discipline, e.g. obstetrics, gynecology, diabetology and are therefore best cared for by the CF center staff.

4.4. Transitional care

A system should be in place to ensure that all children progress to adult centered care in a seamless process. The time of transition to an adult CF center is 16–18 years of age but should be flexible, reflecting the adolescent's social maturity and health status. To guarantee a lifetime continuity of care there must be a close cooperation between the pediatric and adult units including the development of treatment guidelines [31,32].

The cooperation between the Pediatric and Adult CF specialist centers is the cornerstone of successful transition. Therefore cooperation should be focused on continuity of care facilitated by adopting the same diagnostic and treatment protocols, each tailored to specific age groups. Infection control policies should be agreed between the two units to avoid patient and parental procedural anxieties after transfer. There are various models for transition with none proven as optimal. It is recommended, however, that members of the adult multidisciplinary team liaise closely with their pediatric colleagues, and if possible have reviewed the children and parents before the handover of care. The staff from the adult CF center should provide an introduction before transition takes place. Any differences in organization, diagnostic procedures and treatment between the pediatric and the adult center should be clearly documented and presented to the pediatric patient before transition.

As every member of the CF team can impact on the transition process, at the time of transition, all disciplines attached to pediatric care should provide a written report on the patient. On the first day in the adult CF center sufficient time must be made available by the CF specialist to welcome the patient.

4.5. The annual assessment

It has long been established that "the success of treatment will depend upon a complete assessment of the patient and then continuing attempts to obtain normal bodily function and maintain it". [33]. A comprehensive assessment should be performed on newly referred patients and repeated annually [34].

The Annual Review should include all of the following:

1) A history of all medical and life events since the previous annual review. (Immunization status should be established at the 1st assessment. Parents should be advised to allow their children to receive all routine national scheduled vaccinations and an annual influenza vaccination.)
2) A full clinical examination including plotting children's height and weight, and head circumference in young children, on appropriate growth charts.
3) Review by a CF specialist physiotherapist of physiotherapy techniques, competence and frequency of physiotherapy sessions, and use of respiratory therapies (e.g. bronchodilators, rhDNase and nebulised antibiotics). An opportunity to check nebuliser equipment for function and cleanliness. Bronchodilator reversibility testing in patients with airflow obstruction. Some centers also undertake an annual exercise test.
4) Spirometry in patients over 5 years of age, including lung volume measurements in adolescents and adults. Increasingly, younger children are successfully performing spirometry.
5) Nutritional review by a CF specialist dietitian including discussion of a) current diet, b) adequacy and knowledge of pancreatic enzyme replacement therapy, energy and vitamin supplements, c) oral nutritional supplements and enteral tube feeds (where appropriate), and d) weight profile and changes in nutritional status over time.
6) Time with the center social worker and/or psychologist if required.
7) Blood sampling for: full blood count and film; iron status; routinely available inflammatory markers (e.g. ESR, C-reactive protein, IgG); serum electrolytes including sodium, chloride, bicarbonate, calcium, and magnesium levels; glucose; renal and liver function; fat-soluble vitamin A, D, and E levels; prothrombin time; IgE, Aspergillus antibodies (RAST or skin testing and precipitins); *P. aeruginosa* antibodies (if available).
8) Sampling for: fecal pancreatic elastase 1 (in pancreatic sufficient patients only); fecal fat microscopy if there is any evidence of nutritional problems and/or malabsorption; chest X-ray and liver ultrasound; sputum, or cough/throat swab culture.
9) Oral glucose tolerance test in non-diabetic pancreatic insufficient patients aged over 10 years.

10) Surveillance of bone mineral density by dual energy X-ray absorptiometry scanning.

4.6. For patients new to the CF center

1) Repeat sweat test
2) Genotype if not already done
3) Confirm pancreatic insufficiency even if already taking pancreatic enzymes
4) Provide with the center's literature and introduce to all members of the CF team

4.7. Pulmonary function tests

Pulmonary function is an important measure of disease severity and prognosis in CF. Spirometry should be measured at each clinic visit. This includes FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1 s), FEF max (maximal forced expiratory flow), $FEF_{25–75}$ (forced expiratory flow between 25% and 75% of the vital capacity). FEV_1 has been shown to be the strongest clinical predictor of mortality [36] and has been the primary outcome measure in many clinical trials [35]. Other measures of lung function should be available when clinically indicated. Lung function variables are generally expressed as a percentage of a predicted value, calculated using regression equations derived from a reference population. A number of reference equations are in widespread use. It has been shown that among subjects with cystic fibrosis the choice of the reference equation can produce clinically important differences in FEV_1, expressed as a percent of predicted [37]. A large number of spirometeric reference equations that include children are currently used in Europe [38–40]. Disease severity and rate of decline may reflect the choice of the reference equation [37]. Decline of percent predicted values and not in the absolute values can be seen in adolescents in whom the predicted values were changed from the pediatric values to the adult values.

The role of lung function testing during infancy and early childhood remains unclear. Several studies have shown changes in lung volumes and maximal flows indicating early obstruction in the small airways. However, lack of standardized equipment and technique currently prevents routine use of these measurements [41,42].

Cross-infection from pulmonary function laboratory equipment has long been a concern. When a subject performs a forced expiratory maneuver, droplets of oropharyngeal secretions, which may contain bacteria and viruses, are aerosolized. It is recommended that pulmonary function measurements be made in a large ventilated room, with in-line filters, using methods to reduce cross-infection [43] and segregating patients according to their microbial status.

4.8. The newly diagnosed pediatric patient with CF

Most patients with CF are diagnosed before 1 year of age. Within 24 h of the diagnosis being confirmed the CF physician who will be responsible for their medical care should see the patient and parents. A detailed and sensitive explanation of the diagnosis should be given when both parents are present. The improving prognosis, the prospects of new treatments and the need for long-term follow-up should be stressed. The commitment to long-term care by the clinical team should be emphasized and the availability for 24-h advice explained. Contact telephone numbers for appropriate team members should be provided. Patients need to be evaluated for assessment of disease severity and complications and for initiation of the treatment program. The CF education of the family of the newly diagnosed infant, or of the patient and family when the diagnosis is made later in childhood, must begin [44]. This may be done when patients are hospitalized and under the direction of the CF physician and the CF specialist nurse or at home where centers have an appropriate infrastructure of care.

The initial assessment should include a complete history and physical examination, a nutritional review and an SaO_2 measurement. Pulmonary function tests should be performed in patients after 5–6 years of age or at a younger age when possible. Infant pulmonary testing systems may be used where available. Arterial blood gases should be considered in patients with evidence of significant lung disease and a chest X-ray and baseline high-resolution computed tomography scan (HRCT) where considered appropriate. Sputum cultures or cough swabs should be obtained. Induced sputum or bronchoscopy with bronchoalveolar lavage (BAL) may be performed in some centers in children who do not expectorate. Blood tests should include biochemistry including serum electrolytes, liver and renal function, serum albumin, full blood count, clotting studies (PT and PTT), and serum levels of fat-soluble vitamins A, D and E. Acute phase reactants such as ESR, CRP or IgG levels can be used to assess the degree of inflammation. Assessment of pancreatic function should be performed by measurement of human pancreatic fecal elastase 1 and the presence of intestinal malabsorption by one of the semi-quantitative measurements of fecal fat or ideally by a 3-day fecal fat analysis if available.

The education program should begin with a detailed discussion of the disease, including its pathophysiology, organ involvement, complications, rationale of treatment, genetics, and prognosis for morbidity and survival. Attention should be given to correcting any misconceptions and addressing particular concerns. Specific sessions should be held with the child when old enough. Education should be facilitated by visual aids and written booklets. URLs of preferred internet sites should be provided to the patients and families for further reading with reassurance of the willingness of the team to answer any questions. It is important to emphasize the ready availability of the care team. Telephone numbers for daily contact and emergencies should be provided. The treatment strategy should be presented with optimism, emphasizing the success in

preventing or at least delaying complications. The current status of the worldwide research effort and its future direction should be discussed to realistically increase motivation and hope. The entire family may need to be evaluated by the social worker and the psychologist. Specific support should be provided as needed. Open discussion within the family and with the CF team regarding living with CF should be encouraged. Siblings should be sweat tested. (Genotyping of siblings raises important ethical issues i.e. they should have the right to say if they want to know carrier status when they are older and responsible). The families of patients with CF should be offered referral to the genetic service for advice and screening.

The treatment program should be planned and started immediately after the initial evaluation. This should include pancreatic enzyme replacement and fat-soluble vitamin supplementation in patients with pancreatic insufficiency, and correction of any nutritional deficiencies. If the patient has signs of pulmonary involvement (productive cough, tachypnea, pulmonary overinflation, low saturations etc), intravenous antibiotics are usually warranted. Aerosolized beta-agonists, antibiotics, mucolytics and corticosteroids may be used for a limited period of time or continued if felt appropriate. Patients should have their own inhalation machine. Patients and/or their patents should be familiar with its use. In addition, physiotherapy techniques appropriate for the patient's age should be taught and proper technique should be observed before parents take full responsibility for treatment. The center physiotherapist should make contact with a physiotherapist near the patient's home if appropriate to continue treatment after discharge from hospital.

4.9. The newly diagnosed adult patient or patient with atypical CF

Patients who are diagnosed in adulthood usually have milder disease with preserved pancreatic function. Adults have often had symptoms for many years and have been worried by the lack of any diagnosis and proper treatment. The diagnosis of CF might provoke feelings of shock because of associations with premature death. Misconceptions should be corrected and particular concerns addressed. A comprehensive view of CF should be given to the patient with discussion of prognosis. This should consider the late age of diagnosis which is often associated with a milder form of disease. The initial assessment can often be performed in the outpatient setting and should be similar to that in pediatric patients. It should include measurement of serum IgE levels, RAST and precipitins to test for the presence of ABPA (or as a baseline measurement), a documentation of pancreatic function by a 72-h stool collection or by fecal pancreatic elastase 1 measurement, and a glucose tolerance test in patients with known pancreatic insufficiency. Fertility testing (sperm analysis) should be suggested to males who have not presented via infertility clinics with detailed explanation of the cause of infertility and methods available to achieve fertility.

4.10. Management of patients with atypical CF

Atypical CF may be diagnosed in adults with mild single organ disease such as congenital bilateral absence of the vas deferens (CBAVD), sinusitis, nasal polyps, diffuse bronchiectasis, acute and recurrent, or chronic pancreatitis[45,46]. A diagnostic label of atypical CF does not imply the same burden of morbidity and mortality as that associated with the classical CF label. Where only one CFTR mutation is identified an extensive analysis of the CFTR genome in search of a second mild mutation or polymorphism would be of academic interest but is probably not indicated, as it is unlikely to alter clinical care.

Nearly 75% of men with CBAVD have at least one detectable common CFTR mutation [47]. They should be offered CF carrier screening prior to undergoing assisted reproductive techniques; also of equal importance, their reproductive partner should undergo CFTR mutation screening.

Treatment for atypical CF must be individualized. However, it is important that these patients are monitored carefully for early development of any complications and appropriate therapy introduced at an early stage. Until more is known about the natural history of lung disease in patients with atypical CF (isolated CF feature and no chest disease e.g. CBAVD, pancreatitis) these patients should be reviewed every 6–12 months in a CF center and report to the center if they develop any new respiratory or gastrointestinal symptoms.

5. Role of other specialist input into CF care

5.1. Gastroenterology

Determination of exocrine pancreatic function: The assessment of exocrine pancreatic function is a mandatory procedure at the time of diagnosis to determine whether the patient should be given pancreatic enzyme replacement therapy. The secretin-cholecystokinin stimulation test is the gold standard but has major disadvantages. Indirect tests such as fecal fat excretion, breath tests, serum enzyme or fecal determination may be used. Measurement of fecal pancreatic elastase 1 is a non-invasive and simple indirect method to study exocrine pancreatic function. Adequacy of pancreatic enzyme replacement therapy may be determined by assessment of nutritional status; evaluation of signs and symptoms of malabsorption supplemented by stool fat collections as appropriate and semi-quantitative assessment of absorption.

Pancreatitis: Pancreatic sufficient patients may have recurrent episodes of pancreatitis. The cause of abdominal pain in these patients should be investigated by measurements of serum amylase and lipase. Depending on the patient's genotype, gradual exocrine pancreatic function decline may be demonstrated. Consequently, they should be monitored by annual pancreatic fecal elastase 1 measurements and if borderline or abnormal, by quantitative or semi-quantitative fecal fat excretion [48].

Meconium ileus is reported in 10–15% of CF newborns and is usually but not invariably related to exocrine pancreatic insufficiency. In most infants this intestinal obstruction can be successfully treated with hyper-osmolar enemas. In adolescents and adults sub-acute partial obstruction, termed distal intestinal obstruction syndrome (DIOS), may develop. When patients suffer from abdominal pains they should be monitored for stool consistency and frequency. Plain abdominal X-rays may demonstrate dilated small bowel loops, air fluid levels, and a dilated colon filled with fecal material. A CT scan may help in excluding appendicitis or peri-appendicular abscess and intussusception.

Other conditions which may cause symptoms include gastro-esophageal reflux (GERD) and fibrosing colonopathy [49] Celiac disease, inflammatory bowel disease, strictures and adhesions after surgery, and short bowel syndrome can mimic CF gastrointestinal symptoms.

5.2. Hepatology

Early monitoring and regular follow-up for hepatobiliary involvement should include palpation of the liver and spleen at each visit to the CF center. The Annual Assessment should include biochemical liver function tests (aminotransferases, bilirubin, alkaline phosphatase, gamma GT, albumin, prothrombin time, glucose), and a complete blood count for evidence of hypersplenism. Liver ultrasound should be performed annually and should include scoring for hepatic parenchymal irregularity, periportal fibrosis and nodularitiy of the liver [50,51]. Doppler ultrasound gives information about portal blood flow. In special situations additional work-up including MRCP, ERCP, hepatobiliary scintigraphy, upper gastrointestinal endoscopy and liver biopsy are useful [52]. Assessment and regular follow-up of CF related liver diseases (CFRLD) should involve a multidisciplinary team including a pediatrician or internist, a gastroenterologist-hepatologist, a dietitian, a radiologist and a CF-experienced surgeon. The CF center should have established links with a liver transplant unit.

Management of chronic hepatobiliary manifestations includes prevention and correction of malnutrition, early treatment with ursodeoxycholic acid, specific treatment of portal hypertension and liver failure, and liver transplantation. It is important to have emergency arrangements available for the treatment of major GI bleeds, and follow-up sclerotherapy or banding ligation.

5.3. Endocrine pancreatic function

The prevalence of cystic fibrosis related diabetes mellitus (CFRD) increases markedly with age and occurs only in patients with exocrine pancreatic dysfunction [53]. The main pathogenic factor is believed to be disrupted islet architecture due to fibrosis and fatty infiltration of the pancreas. Patients with mild mutations are less prone to developing diabetes. A formal assessment of glucose metabolism in patients over 10 years of age with pancreatic insufficiency should be undertaken annually or more frequently if clinically indicated [53]. The oral glucose tolerance test is the gold standard for the diagnosis of diabetes mellitus and the accepted screening test for cystic fibrosis related diabetes [54]. Patients with established diabetes should have the adequacy of their control measured by serum HbA_{1c}. Routine assessment and review of current drug/insulin therapy, home blood glucose monitoring results, frequency, timing and causes of hypoglycemic and hyperglycemic episodes and understanding of CFRD should also be regularly undertaken. A formal annual review should be undertaken and include screening for complications. An endocrinologist with an interest in CFRD should be involved.

Onset of CFRD is often clinically preceded by weight loss and declining lung function, which are closely linked to residual insulin secretion capacity [55,56]. Only a limited number of patients with CFRD have symptoms of hyperglycemia at diagnosis. As insulinopenia is the cause of CFRD, insulin is the preferred treatment. The decision to start insulin therapy is based on blood glucose profiles and clinical status. Treatment leads to weight gain and increase in lung function, but long-term survival is still reduced [53]. Infectious exacerbations, systemic steroid treatment, and pregnancy are all associated with increased insulin demand due to insulin deficiency. There is limited long-term experience with beta-cell stimulating agents. Patients with CFRD are not protected against late diabetic complications, which must be monitored for regularly [52].

5.4. CF related bone disease (CFRBD)

Cystic fibrosis bone disease is manifest by bone mineral density (BMD)>2 'Z' scores below the age appropriate mean, or by one or more pathological fractures. The underlying problem is low cancellous bone volume, with low bone formation at tissue and cellular level [57]. It is recommended that BMD status is determined during childhood, and especially during the pubertal growth spurt [58,59]. Despite essentially normal nutrition and growth, children with CF may have a worrying reduction in BMD [60]. Possible predisposing factors include deficiencies in vitamin D and K; poor intake of calcium; physiological or pathological reduced exercise performance; delay in puberty; hypogonadism; direct systemic effects of pro-inflam-

matory cytokines spilling from the airway into the circulation; inhaled and oral steroid therapy; and CFRD. Preventive strategies, which should be part of routine CF care, include annual measurement of vitamin D levels and increased supplementation where necessary, and encouragement of a high milk diet and weight bearing exercise, both of which have been shown to increase BMD in other contexts [61,62]. Although there is as yet no evidence for the efficacy of vitamin K supplements in CFRBD routine vitamin K supplementation should be considered [63]. Excessive delay in puberty should be detected and treated. In patients with reduced BMD post pubertal sex hormone levels should be measured and replacement therapy considered in conjunction with a specialist endocrinologist. Whether this will improve BMD is not known.

It is not possible to give evidence-based recommendations as to when and how often to measure BMD. CF osteopenia is silent until the patient has sustained a pathological fracture, and will be missed unless actively sought. Measurement of BMD by dual X-ray absorptiometry is well tolerated and has low radiation risk. BMD should be measured at multiple sites, since there may not be concordant results between sites [64]. In low risk patients BMD should be measured every 2 or 3 years, starting at around age 6 years of age, with more frequent measurements if BMD is low at first examination. High risk groups, in particular those with severe lung disease (FEV_1<50% predicted), high cumulative dose of inhaled or oral steroids, insulin dependent diabetes, and those with a family history of osteoporosis may need more regular measurements of BMD. If it is significantly reduced, and there is no response to simple measures such as dietary manipulation and exercise consideration of biphosphonate and other specific therapies should be made. Furthermore, since osteopenia may worsen after lung transplantation and prejudice the outcome [65] there should be a low threshold for treating transplant candidates.

5.5. ENT complications

Almost all patients with CF will have nasal and sinus disease which is frequently symptomatic. [66] All centers should have a working relationship with the ENT department for the investigation and management of severe sinus disease and nasal polyps. A number of operations including polypectomy, sub-mucus resection including endoscopic sinus surgery, and other complex procedures may be considered. The use of aminoglycosides can have a detrimental effect on the 8th cranial nerve. Collaboration with audiology is important for monitoring of patients, hearing as high frequency deafness is an early indicator of aminoglycoside toxicity. Annual audiological review should be considered for all patients who have had repeated treatments with intravenous aminoglycoside antibiotics. Nasal polyps may cause obstructive sleep apnea, which may contribute to poor weight gain.

5.6. Obstetrics and gynecology

Sexual health is important for all young people. Good general health care information needs to be communicated to all patients who may be sexually active. Expert advice on contraception including barrier methods to avoid HIV and other sexually transmitted diseases should also be made available. There are some specific issues relating to CF that need to be addressed.

5.6.1. Pregnancy in CF

Many women with CF are probably as fertile as non-CF individuals. With progressive loss of lung function and chronic infection there is a reduction in female fertility. Women with CF should have ready access to advice from their CF physician, the CF team and an obstetrician experienced in the management of pregnancy in cystic fibrosis–a link which should be made from all major CF centers. Pregnancy is more difficult in those with an FEV_1 less than 50% predicted and an experienced obstetrician is a key member of the team during this time. [67] Women with CF should be encouraged to discuss their wish to become pregnant with the CF team so preconceptual advice can be arranged.

5.6.2. Fertility

All couples where one or both partners have CF should have a detailed discussion with their CF physician and cover all aspects, including practical and ethical issues, relating to pregnancy. Testing and counseling should be offered to the partner of the individual with CF.

5.6.3. Female infertility

Female infertility should be managed as for women who do not have CF.

5.7. Male infertility

The management of male infertility has been transformed with the introduction of sperm aspiration from the epididymis and intracytoplasmic injection into eggs (ICSI) [68]. CF Centers should have arrangements for referral of couples where the male has CF for further discussion relating to the difficulties and costs of this approach.

5.8. Genetic counseling

Genetic counseling should be available to all newly diagnosed families and their relatives. Counseling should be available to explain the genetic risks for future pregnancies and should be organized for members of the extended family. Genetic counseling should be delivered by a clinical genetic service and provide information and support in an interactive manner. There should be written information available for families to

take home for their information and for other members of their family, who may require further testing [69–71].

5.9. Imaging requirements

Imaging is an important support service for the diagnosis and management of patients with CF. This is primarily focused on the images of the thorax but gastroenterological, liver and urogenital complications of CF also require appropriate imaging. Access to plain radiographs, CT scanning, ultrasound, DEXA and angiography facilities are required by all CF Centers.

5.9.1. Chest radiographs

Chest radiographs are essential in the assessment of children and adults with CF. With the improving prognosis for CF the cost/benefit ratio of cumulative exposure to ionizing radiation needs to be considered. For children it is essential that minimal radiation is used. Children and adults with CF should have an annual chest X-ray and further radiographs should only be taken when there is a strong clinical suspicion of new developments such as an area of pneumonic consolidation, pneumothorax, ABPA or unexplained respiratory symptoms. As the pulmonary disease progresses the chest X-ray becomes less sensitive to change. Various scoring systems are available. We recommend that the Northern CF Score, which only requires a PA film, be used. [72].

5.9.2. CT imaging

High-resolution computed tomography (HRCT) is a valuable method to determine extent and severity of lung involvement in patients with CF. Studies suggest that HRCT might be more sensitive than chest X-rays to detect early and progressive lung disease [73]. However, it is unclear at what age this should be started, and how often it should be done.

CT imaging is also important in the diagnosis and assessment of atypical mycobacterial infection and pneumothorax. CT angiography may be required for the diagnosis of pulmonary collateral arteries in cases of hemoptysis and when pulmonary embolus is being considered. The assessment of sinus disease also requires CT imaging.

5.9.3. Pulmonary angiography

Twenty-four-hour availability of pulmonary angiography and embolisation is critically important for the management of major hemoptysis. As this is often required as an emergency procedure suitable on call arrangements should be made.

5.9.4. Imaging for gastrointestinal and liver disease

Plain films of the abdomen are useful in the diagnosis of distal intestinal obstruction syndrome. Access to lower bowel radiology is also important for the diagnosis and management of this disorder. Urografin/gastrografin enemas are often emergency procedures and should be available at short notice.

Imaging of the liver is important. Regular ultrasounds should be performed to allow early detection of liver disease. For more complex liver problems, CT scanning and/or scintigraphy may also be valuable.

5.9.5. Urogenital disease

Ultrasound images of the vas deferens may be helpful in establishing the diagnosis of CF in atypical patients.

5.9.6. Venous access

In some centers interventional radiologists will insert peripheral lines under ultrasound guidance, or permanent intravenous access devices. In many centers pediatric or vascular surgeons will place the latter. It is important that one or two surgeons become skilled and experienced in the procedure. These options should be available at all CF centers.

5.9.7. Echocardiography

Imaging of the heart is of value in the assessment of pulmonary hypertension. It is also required for lung transplant assessment. Difficulties with totally implanted venous access devices (TIVADs) can be assessed by transthoracic or transoesophageal echocardiography.

6. The cost and staffing of care at the cystic fibrosis center

Nearly all pediatric patients survive well into adulthood and individuals with CF are now surviving into the 4th and 5th decade of life. It is no longer a fatal disease of childhood. The delivery of high standards of care requires an adequate number of staff and facilities for the number of patients attending the center. The cost of care for each patient is lifelong and increasing as survival improves.

The main cost of CF care is related to the lifelong expensive drug usage especially oral, nebulised and intravenous antibiotics. It has been shown that patients chronically infected with *P. aeruginosa* (PA) have a worse outcome than non-infected patients [74]. Aggressive nebulised antibiotic treatment is therefore directed at eradicating PA at time of first acquisition. Healthy patients are often prescribed lifelong nebulised antibiotics and Pulmozyme to minimize and delay disease progression [75]. For patients chronically infected with PA some centers have a policy of treating with 3–4 monthly courses of intravenous antibiotics per year to maintain pulmonary function [76]. As disease severity progresses, many adults will clinically need intravenous antibiotics several times a year to maintain health status. Patients awaiting transplantation can be kept alive for several years with frequent hospitalizations, continuous intravenous antibiotics, over-

night oxygen, non-invasive ventilatory support and tube feeding. Cost of CF care is consequently very high and failure to provide funding and access to good care can result in a worse outcome.

Two studies have specifically evaluated the cost of care delivered from a pediatric and adult CF center [77,78]. Methodology of cost evaluation was different for each study but the conclusions were similar in that there was a greater cost with increasing disease severity. Cost increased threefold for those patients chronically infected with PA and correlated with worse lung function. Cost was not related to increasing age if patients were not infected with PA nor somewhat surprisingly to nutritional status.

The process of funding CF centered care varies enormously within and between countries and will be governed by the different health care systems of those countries. In the UK a banding system according to grades of disease severity has been adopted by adult CF centers and accepted by the Department of Health. However this does not apply to pediatric CF centers nor to every adult CF center. A poll of some CF centers in other countries revealed enormous variation for funding of CF care; Denmark—no limitations, UK—banding system according to grade of disease severity, Australia—block funding by hospital: inadequate funding, Germany—insurance and local support groups, USA—private insurance, medicare (if disabled), CF Foundation according to standard of care.

It is potentially quite easy to define the cost of running a CF center. Each patient will usually be registered on a database. The patients have a chronic disease and each patient's cost can be categorized according to treatment requirements that depend on disease severity. The CF staff required for a multidisciplinary team will depend upon the number of CF patients attending the unit. The annual budget required to run a CF center can be calculated from adding up the costs of care for hospitalization, drugs and staff. This costing method will form the basis for calculating a charging process to obtain an income. Currently, because there is no universal system for funding CF centers within or between countries the income received by the CF center will depend upon local practice (usually government provision or individual patient insurance). Generally, CF centers are inadequately funded.

Patients feel confident when looked after by medical personnel who are experienced in the care of their condition. Cystic fibrosis is a complex disorder and experience and expertise is only acquired by medical personnel working in a CF center. The number of staff required for a CF center will depend upon the size of the patient population at that center. The staff will need to increase in line with the clinic's patient population.

Table 1: illustrates numbers of staff required/50 patients for Specialist Pediatric and Specialist Adult CF centers as recommended by CF Trust UK [6]. Limited resources usually result in underachievement of these recommended figures.

Table 1
The suggested number of whole time equivalent staff (WTE) required for every 50 patients on full care

Staff member	Specialist Pediatric Center	Specialist Adult Center
Consultant 1	0.5	0.5
Consultant 2	0.2–0.3	0.2–0.3
Staff grade	0.4	0.6
Registrar	0.5	0.5
Specialist nurse	1.0–1.5	1.0–1.5
Physiotherapist	0.5–1.0	1.0
Dietitian	0.4	0.4
Social worker	0.4	0.4
Psychologist	0.4	0.4
Secretary	1.0	1.0
Pharmacist	0.3	0.3

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This document is the result of a European Consensus Conference which took place in Artimino, Tuscany, Italy, in March 2004 involving 36 experts in cystic fibrosis, organized by the European Cystic Fibrosis Society, and sponsored by Chiron, Forest Laboratories, Roche, Axcan-Pharma, Genesis Pharma, Bayer, Genentech. The purpose of the conference was to develop a consensus document on standards of care for patients with cystic fibrosis based on current evidence.

Appendix A. Important questions and answers

Definitions can be seen in Table 2.

A.1. What is the minimum diagnostic microbiology service for a CF center?

The laboratory should be able to identify and perform sensitivity testing of the characteristic pathogens found in people with CF using selective media, bearing in mind the often unusual and multiple pathogens. There should be access to a Reference Laboratory to confirm the identification of unusual pathogens and for genotyping and antibody testing where indicated, if these services are not available locally. From the time of diagnosis, respiratory cultures should be performed at every clinic visit and at times of respiratory exacerbations [AIII].

A.2. Under which circumstances should people with CF be separated from each other?

People with CF who are infected with a pathogen which has been shown to be associated with cross-infection (e.g. *B. cepacia* complex, some strains of *P. aeruginosa,* MRSA) should be separated from others with CF both inside and outside the hospital [AII].

Table 2

Definition of categories reflecting the scientific strength of recommendations for or against its use.*

Category	Definition
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate or good evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

Categories reflecting the quality of evidence on which recommendations are based.*

Grade	Definition
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results in uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

A.3. To what extent should people with CF be separated from each other as inpatients on the ward?

When the infection status is unknown, patients should be isolated from other patients with CF. They should preferably remain in single rooms. Once their infection status is known, if single room accommodation is not available, patients with the same microbiological status on very recent sputum tests (cohort isolation) may share a room, although the emergence of transmissible strains may make cohort isolation unreliable [AII]. Patients with CF may share rooms with non-CF non-infectious patients. In all circumstances the highest standards of hygiene should be employed.

A.4. To what extent should people with CF be separated from each other in the outpatient clinic?

Patients attending the clinic should be segregated according to their microbiological status (see 2)—ideally attending on different days [AIII].

A.5. Should suspected B. cepacia complex organisms be confirmed in a reference laboratory?

All organisms identified as being of the *B. cepacia* complex should be confirmed at a Reference Laboratory and their genomovar established in order to prevent cross-infection [AIII].

A.6. Should all P. aeruginosa isolates be typed to establish the presence of an epidemic strain?

Preferably, the *P. aeruginosa* from every chronically infected patient should be genotyped [AIII].

A.7. What is the role of the microbiologist in the CF team?

In addition to providing a laboratory service and advice on infection control, the microbiologist should participate in regular multidisciplinary meetings with other members of the CF team to discuss the management of individual patients [AIII].

A.8. Do patients treated in CF centers have a better prognosis than patients treated by general pediatricians and physicians?

Yes. Adults with CF who have received both pediatric and adult center care have a significantly better FEV_1, BMI and CXR score compared with those who have not received center care [BIII]. Center care is associated with better survival [BIII].

A.9. Should neonatal screening be available universally?

Yes.

Screened infants have nutritional and respiratory advantages. Weight, height, and head circumference are more likely to be within the normal range and nutritional advantage appears to continue throughout childhood [BIII]. Identification by neonatal screening allows early referral to a CF center to ensure optimal treatment is started, which is essential if the benefits of screening are to be realized [AI,BIII]).

Early diagnosis allows the parents to make informed decisions with regard to further family planning.

A.10. How often should patients with CF come for routine check-up?

The frequency of clinical review by the CF team should reflect the age of the patient and the severity of the disease. The patient should be seen routinely every 1–3 months. More frequent monitoring in the CF center is associated with a better outcome [BIII]. Newly diagnosed infants or patients with severe disease may need to be seen at weekly intervals. Adult patients with atypical CF and normal lung function may be seen less often [AIII].

A.11. Do all annual reviews need to be done in a CF center?

Yes. The annual review should be performed in the CF center. This allows specialist input from the CF team with expert review, for example, of physiotherapy techniques, nebulizer cleaning practices, diet and pancreatic enzyme supplement dosage [AIII].

A.12. Where should all laboratory tests be performed?

Where national standards for laboratory performance exist, results from non-center hospitals for tests based on

blood samples can be relied on. Sputum microbiology should be performed in an accredited CF center at least once per year and whenever an unusual organism or pathogens such as *B. cepacia* complex are cultured [AIII].

A.13. Who is responsible for patients who receive shared care?

Where shared care exists, it demands effective communication between the satellite clinic and the center. The day-to-day care should be the responsibility of the local consultant. The center should be involved at an early stage whenever the patient is not responding to routine therapy or when there are complications. Transfer of the patient to the center should be considered at such times [AIII].

A.14. Should we use universal standards for pulmonary function tests?

Universal standards for pulmonary function are an essential prerequisite for comparison between centers and meaningful data entry to a European database. National centers must use the same methodology. Agreed standards have been published [AIII]).

A.15. Who should be the primary members of the CF team?

- Pediatrician or adult physician: Center director+CF Specialist (pneumonology/gastroenterology)
- Nurse specialized in CF care
- Physiotherapist
- Dietitian
- Social worker
- Psychologist
- Clinical pharmacist
- Microbiologist
- Secretary/Database manager

[AIII]

A.16. Should all patients with exocrine pancreatic insufficiency be routinely seen by a gastroenterologist?

Not routinely. Generally management of pancreatic insufficiency can be achieved by the CF physician and the CF dietitian [AIII].

A.17. Should patients with pancreatic sufficiency be routinely evaluated for exocrine pancreatic function? If yes how, and how often?

Yes. Up to 4 years of age a test of exocrine pancreatic function should be done every 6 months in patients with pancreatic sufficiency. In older children exocrine pancreatic function should be evaluated if failure to thrive, weight loss or symptoms suggestive of malabsorption occur. Fecal pancreatic elastase 1 determination is the method of choice for this purpose. Routine evaluation should be part of the annual assessment [AIII].

A.18. Do we need to monitor efficacy of enzyme treatment in patients with exocrine pancreatic insufficiency? If yes how?

Yes. Regular evaluation of malabsorption symptoms and signs is mandatory. The gold standard for assessing efficacy of enzyme treatment is a fat balance study. Although semi-quantitative tests e.g. fecal fat microscopy, are less reliable, they are more practical for routine assessment of the efficacy of pancreatic enzyme replacement therapy [AII].

A.19. What routine screening should be performed for CF related liver disease? How frequently should these be done?

Palpation and percussion of liver and spleen should be done at all clinic visits. Biochemical evaluation should be performed yearly in all patients and should include aminotransferases, bilirubin, alkaline phosphatase, gamma-GT, albumin, and prothrombin time. A complete blood count should be performed to assess for signs of hypersplenism. Other causes of liver disease should be excluded. Liver ultrasound should be considered annually [AII].

A.20. When, how and how frequently should patients be screened for diabetes mellitus?

Patients with CF with exocrine pancreatic insufficiency should be screened annually for diabetes mellitus from the age of 10 years with the modified oral glucose tolerance test. However, insulin deficiency has been described below the age of 10 years. Assessment of glycemic status may be indicated between annual reviews in patients with unexplained weight loss or respiratory deterioration, those on steroids or enteral tube feeding and in women planning a pregnancy. Screening for diabetes should also be done during pregnancy (before 28 weeks gestation) [AII].

A.21. Should patients be screened for CF bone disease?

Bone mineral measurement may be necessary from the age of 10 years. Screening for bone disease can be done by dual X-ray absorptiometry (DEXA). Measurements should be done every 2–3 years or more often if indicated. [AII].

A.22. When and how should a CF patient be transferred to the adult clinic?

WHEN?

Transition to adult care should take place during emerging adulthood, 16–19 years.

The age of transition should be flexible but completed by 19 years.

Transfer may be occasionally delayed or accelerated for psychosocial or medical reasons e.g. transplantation or developmental delay [AIII].

HOW?

The idea of transition to adult care should be introduced soon after diagnosis. All patients and their parents should have the opportunity to meet the adult team prior to transfer. A written joint policy should be developed between adult centers and referring pediatric clinics. Joint clinics between the teams from age 15–19 years are a valuable transitional arrangement. A transfer report including details of diagnosis and subsequent care from all key team members and issues of special importance to the patient and parents should be provided [AIII].

A.23. In what circumstances is care in a pediatric clinic acceptable for the older patient?

Where an adult CF center is available prolonged care in a pediatric center is only acceptable in cases of terminal illness [AIII].

A.24. Should adult physicians be part of the Pediatric CF team?

The involvement of an adult physician in the pediatric team is not an acceptable replacement for an adult center. Close cooperation between the pediatric and adult teams is mandatory [AIII].

A.25. Who has the responsibility for developing adult care centers?

An alliance between physicians/pediatricians, parents, adults with CF, patient associations and national medical and scientific societies should work with local health-care purchasers to develop adult centers. The development of the center will usually be the responsibility of a pulmonologist who has additional training in CF care[AIII].

A.26. Is there a role for a general practitioner or general pediatrician in the care of CF patients?

As CF is a complex disease requiring specialist care, the direct role of the GP in CF management is limited. The GP may have an important role in supporting the family. Good communication between the hospital and GP is important. All changes in CF treatment should be approved by the CF center [AIII].

Under the initiation and direction of the CF center, local pediatricians, physicians or GPs may be involved in a supportive role by providing practical arrangements for the delivery of care.

A.27. How should results of X-rays be documented? By free text or by a scoring system?

Longitudinal comparison of chest radiographs is important. This is achieved by direct inspection of radiographs and may be assisted by a scoring system [AII].

A.28. How should progression of lung disease be routinely assessed in different age groups?

0–6 years
Every visit
Symptoms and signs of pulmonary disease
Height and weight chart
Sputum culture/cough swab
Spirometry as soon as possible
Oxygen saturation
Annually
Chest radiograph (Scored)
Infant pulmonary function tests when available

Over 6 years
Every visit
Symptoms and signs of pulmonary disease
Spirometry.
When FEV_1<50% predicted then $Sa0_2$ is mandatory
Weight and height.
Sputum culture or cough swab
Annually
Lung volumes
When FEV_1<50% predicted capillary $PaCO_2$ measurement is indicated
Chest radiograph (scored)
[AIII]

A.29. How many patients can one full time CF physician or other CF team member take care of?

One full salary equivalent per 50–100 patients depending on the age of patients, complexity of disease and outpatient and inpatient requirements [AIII].

A.30. What should be the minimal size of a CF center?

A CF center should be of a sufficient size to facilitate and justify a multidisciplinary team approach to 24-h care and provide CF research, training and teaching. To allow for the development of expertise the clinic size should be a minimum of 50 children or 50 adults [AIII].

A.31. What are the direct costs of CF care?

The costs of CF care are composed of:

Maintenance of the CF multidisciplinary team and facilities

Services provided at routine clinic visits and outpatient care

Routine medical/nutritional treatments
Hospital admissions (exacerbations, surgical procedures, psychosocial care, pre/post natal care etc)
End of life care
Organ transplantation
Healthcare costs are related to age and disease severity. [AIII]

A.32. How should CF centers be financed?

CF center funding should cover hospital and community costs. CF care is increasingly expensive due to the complexity of the disease and the growing adult population. The financing of CF centers and care should not be borne by patients and should be a national responsibility. How to accomplish this will depend on the healthcare system of each country [AIII].

A.33. Does every CF center need to have a database?

The database is an essential tool in the management of CF. Every patient with CF should be part of a local and national database and the CF Team should have access to the former information to allow for local decision making and research [AII].

A.34. Should every CF center offer home intravenous antibiotic therapy?

CF Centers should offer home IV therapy and establish criteria for its use. When appropriate, home IV therapy can improve quality of life, reduce the risk of cross-infection and reduce the cost of care [AII].

A.35. What is the responsibility of the CF center when pediatric or adult patients repeatedly fail to attend appointments?

It is the responsibility of the CF Center to try to understand and resolve the underlying reasons why pediatric or adult patients repeatedly fail to attend appointments.

Adult patients are free to make their own decisions but need to be made aware of the potential consequences of their choice.

When intervention by the pediatric CF team social worker and psychologist has failed to resolve the problem, the CF center should consult with the childcare authorities [AIII].

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