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Coming of age in cystic fibrosis – transition from paediatric to adult care

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ABSTRACT – Cystic fibrosis (CF) is the most common multi-system inherited disorder, with a UK population exceeding 9,000. There have been significant improvements in CF survival over the decades, attributed to improvements in therapies available, our understanding of the disease and better organisation of care. CF care providers have been early advocates for successful health-care transition from the paediatric to adult sector and CF can be considered a model process where a paediatric disease has now become an adult one. This article looks at the transition process in CF and the future challenges CF physicians will face.

KEY WORDS: Cystic fibrosis, transition, CF survival

Introduction

Cystic fibrosis (CF) is the most common multi-system inherited disorder in the western world, with a prevalence of 1 in 2,500 Caucasian live births and a UK population already exceeding 9,000. It has classic Mendelian autosomal recessive inheritance, with a carrier-gene frequency of 1 in 25. Mutations in the cystic fibrosis trans-membrane regulator (CFTR) gene product and subsequent ion transport abnormalities at mucus-producing cell surfaces result in thick mucus and end organ damage, most apparent in the lung and pancreas but affecting all exocrine organs.

There have been significant improvements in CF survival since the 1930s, when 70% of sufferers died in infancy, to a median predicted survival in 2011 of 41.5 years.[1] Early CF deaths are now rare: more than 95% of children with CF enter adulthood[2] and those born with CF in this century can expect to survive into at least their sixth decade.

This dramatic improvement in survival is attributed to enhancements in screening, nutrition, drugs, paediatric and adult care, socio-economic factors and psycho-social support. Since the first description of CF in 1938, each decade has seen key developments. In the 1940s, Paul di Sant' Agnese demonstrated that CF infants presenting with heat stroke had a five-fold excess of sodium and chloride in their sweat. In the same decade, the multisystem nature of the disease was established and, shortly after the discovery of penicillin, children who were given the new drug had greater chances of survival. The 1950s saw the development of practicable, safe and accurate sweat testing, with the use of pilocarpine iontophoresis to permit a firm diagnosis of the disease, and the emergence of new infection with bacteria such as *Pseudomonas aeruginosa* (*Psa*). The 1960s saw the benefits of physiotherapy improve as techniques developed and gained widespread acceptance, along with the introduction of mucolytic therapy. Thanks to strong parent and support groups, the 1960s also saw the formation of the Cystic Fibrosis Research Foundation Trust in the UK (now the UK CF Trust), the European Working Group for Cystic Fibrosis (now the European CF Society) and the US CF Foundation (CFF), which was started by a group of volunteer parents in Philadelphia. Nevertheless, the prognosis was still poor, with those children reaching school age classed as 'survivors'. The 1970s saw the development of specialist CF centres, offering care to individuals who were surviving longer, and developments around nutritional needs. The 1980s saw the expansion of CF centres in the UK and the earlier use of intravenous antibiotics coupled with the emergence of antibiotic resistance. The basic genetic defect was identified in 1989,[3] a breakthrough that has pioneered our modern understanding of the disease.

Box 1. Cystic fibrosis-related complications and associations.

Pulmonary
- Chronic infection
- Bronchiectasis
- Pneumothorax
- Oxygen dependence

Gastro-intestinal disease
- Constipation and obstruction
- Nutritional difficulties
- Liver and gall bladder disease
- Reflux and decreased motility

Psycho-social
- Depression
- Anxiety
- Adjustment disorders
- Substance abuse and addiction
- Relationship problems
- Work-related difficulties

Treatment issues
- Treatment burden
- Compliance
- Phobias (eg needle phobia)

Other related conditions
- CF-related diabetes
- Osteoporosis
- Male infertility

CF = cystic fibrosis.

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The 1990s were associated with steady developments towards improvement in clinical care and the realisation of new problems: cross-infection, the identification of *Burkholderia cepacia* infection as a rare but life-threatening complication and the need for segregation. At the same time, with improving survival the unforeseen complications of liver disease, diabetes and osteoporosis were becoming more prevalent.

Following the millennium, progress has been made in gene therapy, and following successful clinical trials, new drugs (eg ivacaftor) have become available to treat the basic genetic defect in some individuals. These developments in gene therapy are expected to modify the course of the disease and further improve survival in this unique patient group.

In the UK, in 2002 CF truly 'came of age', when the number of CF adults (of 16 years of age or older) equalled the number of those in childhood; by 2010, adults made up 56% of the CF population (Fig 1).[1] Deaths in childhood are now rare: the median age of those with CF at death is 26 years,[1] leading to a net increase in the adult CF population of about 145 patients each year.[2]

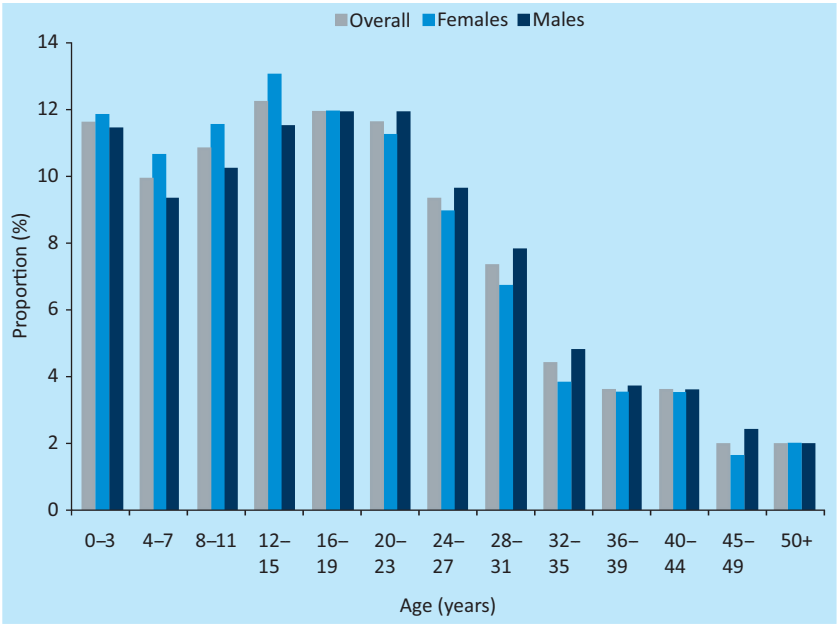

Fig 1. Age distribution of UK CF patients. (Reproduced with permission of the Cystic Fibrosis Trust).[1]

Against this background, those providing CF care have been early advocates of supporting individuals through a successful healthcare transition from the paediatric to the adult sector. CF can be considered a model for the process through which a paediatric disease has now become an adult one. This article looks at the transition from paediatric to adult care in CF, and the future challenges CF physicians will face.

Spectrum of cystic fibrosis disease

CF patients are faced with a number of CF-related complications and associations, broadly divided into medical, treatment-related and psycho-social (Box 1).

Transition in cystic fibrosis

Transition from child-centred to adult healthcare systems is important for all teenagers, healthy or ill, and an understanding of adult services is vital for successful disease management. Paediatric services foster a nurturing and prescriptive atmosphere.[4] By contrast, adult services focus on the individual, and not the parents or carers, and patients are expected to have autonomy in making decisions about their health and to collaborate with treatment providers.

With improving survival, the spectrum of pulmonary and non-pulmonary complications has shifted towards the older CF population: paediatric practice is increasingly focussed on disease prevention, while adult clinicians are faced with chronically ill individuals for whom disease management is more important. The differing models of healthcare currently offered in the UK reflect this: children are often cared for in local specialist clinics that are convenient geographically for parents and carers, working under formal 'shared care' arrangements with a regional specialist centre. Shared care is not, however, a recommended model in adult CF, where patients often have more complex needs and are less dependent on carers: the move from a paediatric to an adult centre might involve shifting care away from a hospital geographically closer to home to one further away, and this has to be factored into the transition process.

In CF, the topic of transition is introduced well before transfer might be expected to take place, usually in the very early teenage years, allowing time for the young person to adapt and resolve their and their parents' or carers' concerns. Paediatric consultations at this important time progressively focus on the young person, but do not exclude parents prematurely or abruptly. The process should also provide opportunities for the young person to familiarise themselves with the new staff and the new environment on an informal basis, and many adult UK CF centres have transition 'open days' to facilitate this.

Time of transition

The actual timing of transition and transfer to adult services is flexible. In the UK, the CF Trust recommends that broad age limits be set.[5] This period and process comes with concerns and expectations and is a stressful time for patients, families and carers because of the introduction of an unfamiliar environment, fear of change, potential exposure to new pathogens and the beginning of taking the responsibility for one's own health.

Addressing the concerns and expectations of patients and family members is the most important factor in the process, owing to the sometimes challenging hurdle of negative attitudes. The two most important concerns usually identified by CF patients prior to transition are the potential exposure to infection and having to leave their previous caregivers.[6] This time of

Table 1. The Liverpool Model for cystic fibrosis patient transition.

Age (years)	Process	Key points
13	Patient preparation	• Adolescents start attending the paediatric clinic on their own
16–17	Assessing patient readiness	• Offered individual visit to the adult centre (open day) • Paediatric hospital liaises with adult centre to establish when the patient is ready for transition
17	Coordination	• CF nurse specialists (CFNS) lead coordination between the two centres
	Nursing summary	• Document produced for each patient • Joint CFNS meeting pre-transition
	Medical summary	• Referral letter outlining care since the patient commenced attending paediatric service
	Primary care services	• Paediatrics liaise with the primary care team about readiness to transition
	Joint clinic	• First appointment at adult centre • Led by adult care providers • Paediatric team invited to attend • Patient introduced to all members of the multidisciplinary team
	Patient follow-up	• Offered home visit by CFNS • Routine clinic appointment without paediatric team
	Evaluation	• Questionnaire detailing process sent to patients and carers
	Annual review	• Never done on first visit but done during subsequent visit • Blood tests done early after the transition clinic

CF = cystic fibrosis; CFNS = cystic fibrosis nurse specialists.

transition also occurs when important adolescent issues, including relationships, fertility and rebellion, are prevalent, and the development of trust in a new team and a feeling of loss of control over their child's illness is also challenging for parents.

CF model of transition

The preparation for transition from paediatric to adult care is critical. Paediatricians and adult CF physicians are well aware of the challenges of ensuring that this unique group of patients continue to receive appropriate therapies as they begin adulthood, and have led on developing models of transitional care over the last few decades.[7,8]

The CF transition program is patient centred, allowing them to retain a degree of control over the speed of transition within predefined limits. A number of models of transition care exist but the most common model, the recommended standard in the UK,[5] has paediatricians 'handing over' care at an adult CF centre. This process often occurs in the manner of a joint clinic with the paediatrician, with whom the young person has a good relationship, and adult physicians in attendance; there are also opportunities to meet other members of the adult team accompanied by their paediatric counterparts. Such clinics, managed sensitively, focus around how the young person's care has been and will be managed, taking into account individual needs and concerns. In some centres, adolescent clinics have been developed to ease this transition process.

Irrespective of which model of transition is adopted by a CF unit, the arrangements must be clear for both patients and their carers, and care should be delivered as appropriate to their needs. There is, however, no 'one size fits all', and each region will develop a different model that suits the needs of adolescent healthcare users, bearing in mind the constraints placed by integrating their care into an existing adult provider service.

An example of the transition process – the Liverpool Model

Paediatric CF services for the area around Merseyside (including North Wales, parts of Cheshire, and the Isle of Man) for 313 patients are supervised by the regional centre based at Alder Hey Hospital, which has shared care arrangements with 11 clinics in district general hospitals. The adult service is provided by one large regional adult CF unit at the Liverpool Heart and Chest Hospital, set up in 1993, which now caters for 280 individuals from throughout the region.

Our transition program involves three phases: pre-transition, transition and post-transition.

Paediatric teams from around the region identify patients in their early teens for transition, introduce the topic and set out an appropriate timetable. These patients are then sent a patient-friendly transition booklet, which outlines the service and process, and informs patients of the strict segregation policy to prevent cross infection that applies to all CF patients. In the year before the intended transition, multi-disciplinary team members from adult and paediatric services meet and discuss the care of each transitionee. The patients themselves are contacted and offered an informal visit on an individual basis to familiarise themselves with the adult service facilities.

Patients are then formally handed over by their paediatrician to a CF adult physician at a series of joint clinics held each year at the adult centre; patients attend at least two of these clinics and possibly more, taking into account their microbiology status.

During the joint clinics or at subsequent visits, the patient and their family are encouraged to meet other members of the multidisciplinary team. The process is described in more detail in Table 1.

Challenges for adult CF physicians

With increasing survival come new complications, either as previously unexpected manifestations of the CF condition or as a consequence of a lifetime of necessarily aggressive treatment regimes. Some challenging areas for CF physicians are outlined below.

Fertility and pregnancy

Nearly all males with CF have under-developed or absent vas deferens and are azoospermic,[9] but the availability of mesenteric

sperm aspiration means that increasing numbers are now capable of fathering children. Although there is evidence that CF females may be sub fertile as the result of thick cervical mucus,[10] in practice, many achieve pregnancy and immediate outcomes are favourable if lung function is >50% predicted.[11] The long-term consequences of reproduction still need to be considered by CF parents as significant CF-related mortality still occurs in early adult life, and they risk leaving their children without parental support. All young CF adults are encouraged to discuss their wishes for reproduction with the CF team so that appropriate counselling can be offered.

Cystic-fibrosis-related diabetes

Diabetes in CF is becoming increasingly important, with an adolescent prevalence of 20% and up to 50% in adults. Cystic-fibrosis-related diabetes (CFRD) is unique and distinct from other types of diabetes, with few CF patients having truly normal glucose metabolism. It is associated with increasing age, worse pulmonary function, under-nutrition, liver dysfunction, steroid use and a six-fold increase in early mortality. Decline in weight and lung function precede the diagnosis of CFRD by current criteria by months to years.[12–14] Early insulin initiation delays a decline in lung function by an average of 34 months.[15] The biggest problem facing CF physicians is the lack of a satisfactory screening tool to facilitate the early diagnosis of CFRD. The traditional diagnostic oral glucose tolerance test (OGTT) uses glucose thresholds derived from a non-CF population to prevent micro-vascular complications. In CF, however, glucose handling is variable and a single OGTT can be misleading. Newer, more physiological methods, such as continuous glucose monitoring (CGM,) are gaining popularity but the early recognition of CFRD remains problematic.

Renal disease in CF

Renal disease is becoming increasingly recognised as a feature of CF because CF patients are repeatedly exposed to a number of nephrotoxic drugs, many administered at relatively high doses. The two most common drug causes of renal dysfunction in CF are aminoglycosides and immune suppressants used post lung transplant. Renal impairment in CF is difficult to diagnose by traditional methods (eg formulae estimating creatinine clearance) and we have shown these to be inaccurate in assessing renal function in CF patients.[16] Adult and paediatric CF physicians continue to work on strategies to limit the effect of nephrotoxic drugs on the kidney.

Cross-infection and segregation

Most CF patients have chronic lung infections and cross-infection causes a high level of concern for both paediatric and adult CF physicians because microbiological status has a high impact on quality of life. In adult clinics, *Pseudomonas aeruginosa* (*Psa)* is the most common organism (Fig 2),[1] and increases in prevalence during the teenage years. Other pathogens responsible for cross-infection are methicillin-resistant *Staphylococcus aureus* (MRSA) and *Burkholderia cepacia.* Despite efforts to reduce cross infection, the transmissibility of some strains of *Psa* between patients (particularly the Liverpool Epidemic strain (LES)) is worrying. LES is now widespread in UK CF clinics[17] and elsewhere.[18] It is associated with increased morbidity and decline in lung function, and is also more antibiotic resistant.[19] Preventing the spread of these organisms requires expert microbiological surveillance and adequate cross-infection control that taxes inpatient and outpatient resources.

Bone health problems

A number of factors can lead to reduced bone mineral density (BMD) in CF: calcium and vitamin (D and K) deficiency due to malabsorption, reduced weight-bearing activity, delayed puberty, steroid use and chronic inflammation. In addition, the presence of CFTR in bones might lead to increased resorption and further bone thinning.[20] Up to 24% of adults have osteoporosis.[21] The associated fracture risk (up to 14% for vertebral and 20% for non-vertebral fractures)[21] complicates their ability to tolerate adequate mucus clearance techniques and can be associated with a decline in lung function.

Biphosphonate use increases an already heavy treatment burden and can be associated with increased bone pain.

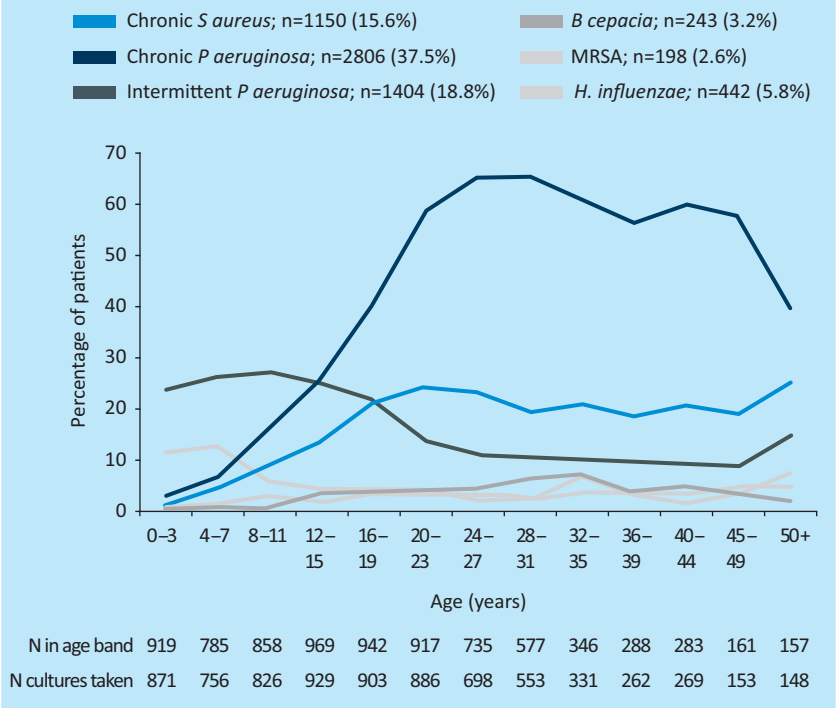

Fig 2. Lung infections in cystic fibrosis patients. (Reproduced with permission of the Cystic Fibrosis Trust).[1] MRSA = methicillin-resistant *Staphylococcus aureus*.

Staffing issues

Within the UK, the medical curricula for undergraduates and postgraduates do not focus sufficiently on young people's health. In addition to a lack of training in adolescent medicine, there are considerable differences between paediatric and adult CF program directors' perceptions of the concerns that CF patients, their families and the medical teams have about transfer. Flume *et al*[22] found a correlation between the physician's perceptions of the process and their perception of the success of a transition program. Many adult centres are struggling to cope with the growing adult CF population, and adequate training of adult respiratory physicians and other multi-disciplinary team members is one factor inhibiting the development of new centres. A recent survey showed that large proportion of respiratory specialist trainees in the UK have limited exposure to CF, with only 55% rotating to a CF centre despite alterations to the specialist training curriculum.[23]

Conclusions

The next few years will see many more challenges for paediatric and adult CF physicians. CF care is costly and there will be pressures to reduce expenditure that might impact on the delivery of a high standard of care, despite the need to invest in more centres with more training in CF care for physicians. An ageing CF population will bring increasing multi-system complications, including osteoporosis, renal disease and diabetes. Although gene therapy brings promises of a cure, this is at a very high cost and will not address the existing structural damage caused by years of disease.

The optimisation and delivery of a high standard of care and the close working of both paediatricians and their adult counterparts is, and should remain, the main focus for managing this life-long disease.

The transition process for each individual should culminate in the successful transfer to and full integration within the adult CF service, where appropriate high-quality care will continue to be delivered. Although continuously evolving, the process should be multi-factorial, coordinated, and gradual; it should involve professional caregivers, the young person and their family.

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