Changing epidemiology and clinical issues arising in an ageing cystic fibrosis population

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Abstract: Improvements in the quality and implementation of medical care for individuals with cystic fibrosis (CF) have resulted in a dramatic improvement in survival. Many of these strategies have focused on the effective management of pulmonary disease which has delayed its manifestations into later years. With an increasing number of patients surviving to later years the impact of chronic inflammation and nutritional compromise on other organ systems over a lifetime are increasingly manifest. This review highlights the changing epidemiology of the ageing CF population and the complications that may ensue.

Keywords: ageing, CF-related diabetes, cystic fibrosis, epidemiology, malignancy, osteoporosis, pancreatitis, renal disease, stress incontinence

Introduction

Survival rates for individuals with cystic fibrosis (CF) have steadily improved since the disease's initial description in 1938 when most patients did not survive beyond their first year of life [Andersen, 1938]. In 2008, the median survival of CF patients in the UK was 38.8 years [Cystic Fibrosis Trust, 2009]. The improved survival in CF has been attributed to a number of interventions including improved diagnostics and screening [Farrell *et al.* 2001], improved nutritional management and availability of pancreatic enzyme replacement therapies [Kalnins *et al.* 2007; Corey *et al.* 1988], development of specific and specialized physiotherapy regimens [McIlwaine and Davidson, 1996], the consolidation and specialization of CF care at regional centres [Merelle *et al.* 2001; Mahadeva *et al.* 1998], and the availability and effective use of antipseudomonal antibacterial therapies [Smyth and Elborn, 2008; Bell and Robinson, 2007]. Further improvements in survival are anticipated as there is a significant pipeline for the development of CF-specific medications [Ashlock *et al.* 2009; Goss *et al.* 2002]. Recently, the improved understanding of the pathogenesis of CF, from the molecular defect to the natural history of chronic lung infection, has identified new modalities and strategies for treating patients. Accordingly, there is every reason to believe that these trends of improved survival noted over the last four decades will continue to occur for years to come. It is now estimated that a child born today with CF will survive into their fifties [Dodge *et al.* 2007].

Despite these improvements, children and adults with CF continue to live with a life-limiting and increasingly medically demanding disease, though most of the morbidity and almost all deaths have been shifted to adult years. With the improved longevity observed in CF patients, new management challenges, both therapeutic and psychosocial, face CF clinicians. Complications which are relatively unique to the aged CF population owing to a lifetime of chronic infection and inflammation, nutritional compromise and respiratory muscle fatigue have begun to emerge. In this review we discuss the available evidence regarding the epidemiology of the ageing CF patient, natural history of CF in the adult patient and highlight some of the more serious complications faced by these individuals.

Epidemiology of CF

The diagnosis of CF, particularly in those individuals presenting on clinical grounds in adolescence or adulthood, is often complex. A consensus guideline with diagnostic criteria for determining CF has been published recently [Castellani *et al.* 2008; Farrell *et al.* 2008]. It is, however, evident that CF is a heterogeneous disease with a widely variable clinical phenotype. Individuals presenting with classical (typical)

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CF have pancreatic insufficiency, associated nutritional compromise, and bronchiectasis. As a result, these individuals are usually diagnosed early in life. Individuals presenting with nonclassical (atypical or mild) CF often have a milder phenotype with pancreatic sufficiency, less lung disease and may not present until adulthood. Furthermore, there is a subset of individuals who fail to meet diagnostic criteria for CF. They have normal or intermediate sweat chlorides, one CFTR mutation and manifest disease in one organ system, and are referred to as having CFTR-related disease [Goubau *et al.* 2009; De Boeck *et al.* 2006]. As the outcomes of this group are expected to be markedly superior, it is important that clinicians correctly distinguish CF patients from those who merely have CFTR-related disease.

The development of large longitudinal national (the Cystic Fibrosis Foundation National Patient Registry in the US, the United Kingdom CF Patient Database from the Cystic Fibrosis Trust and the Canadian Cystic Fibrosis Foundation Canadian Patient Database) and international (European Epidemiologic Registry of Cystic Fibrosis) patient registries to follow the progress of CF lung disease has allowed for insight into the changing disease course, prognosis and risk of future complications. The continued improvements in survival for individuals with CF have clearly been observed and documented independently in multiple cohort studies including those from the United States [Kulich *et al.* 2003], Canada [Corey and Farewell, 1996] and Europe [McCormick *et al.* 2010; Bellis *et al.* 2007; Dodge *et al.* 2007]. Whereas older studies involving cohorts of CF patients demonstrated significant variability in survival between different countries [Fogarty *et al.* 2000] recent comparative analyses have shown that these differences in countries with similar levels of healthcare spending have narrowed and almost disappeared [Buzzetti *et al.* 2009]. However, in those countries with limited healthcare spending, deficits persist [McCormick *et al.* 2010].

Today it is an expectation that a child born with CF will survive to become an adult. This has had a tremendous impact on the disease. Whereas CF has always been considered a disease of childhood, the paradox now exists that more individuals with CF are in fact adults. From 1982 to 2007 the proportion of individuals with CF achieving adulthood (>18 years of age) increased from 27% to 56% [Cystic Fibrosis Foundation, 2008]. Even the proportion of CF individuals reaching middle-age status has increased. CF patients in their twenties account for 22–24.6%, thirties 12–14% and forties or older 7.2–10% of the total CF population [Cystic Fibrosis in Australia, 2008; Cystic Fibrosis Foundation, 2008]. Indeed, for the first time median survival has been reported in one patient registry at >40 years. In the Canadian Cystic Fibrosis Patient Data Registry Report median survival improved from 37.3 in 2002 to 47.7 in 2007 [Cystic Fibrosis Foundation, 2008]. Despite improvements in care, the sobering fact remains that median age of death for individuals with CF remains 27–32 years [Cystic Fibrosis in Australia, 2008; Cystic Fibrosis Foundation, 2008; Cystic Fibrosis Trust, 2008]. The most common cause of death remains respiratory failure.

Individuals with end-stage CF may undergo life saving lung transplantation surgery and have improved survival [Liou *et al.* 2001; Aurora *et al.* 1999]. The availability of transplantation continues to be regionally dependent with the ratio of transplants to deaths ranging from 0.17:1 in the UK, 0.37:1 in the US, 0.68:1 in Australia and 0.9:1 in Canada in the most recent year of reporting [Canadian Cystic Fibrosis Foundation, 2007; Cystic Fibrosis Foundation, 2008; Cystic Fibrosis Trust, 2008]. It is well recognized that lung transplantation does not cure disease but rather exchanges CF chronic lung disease for another medical condition. Furthermore, the CF phenotype in other organs persists posttransplant. It is interesting to note that survival outcomes do not differ to the same extent as transplant availability confirming that improved pretransplant care continues to be the major catalyst for increasing CF longevity.

Epidemiology and clinical features of the ageing CF cohort

The relative makeup of the ageing CF population changes with age group. This is most evident when looking at markers of disease stratified by age category. Lung function values by age cohort steadily decline until the mid-twenties and then stabilize [Cystic Fibrosis Trust, 2008]. Furthermore, BMI values steadily increase with each age cohort in adults. The most obvious explanation for this phenomenon is the survivor effect. Individuals with more advanced disease are more likely to die or receive transplantation.

As such, the relative contribution of individuals with milder disease phenotypes or those who have received bilateral lung transplants may be increased in long-term survivors. Furthermore, with the increased availability of genetic testing and a greater appreciation for the diverse clinical spectrum of CF, this diagnosis is increasingly occurring in adults. Whereas adult diagnoses comprised less than 3% of cases identified in the CFF registry in 1982, this had risen to 9.9% in 2002 [Nick and Rodman, 2005]. To further explore this, several investigators have sought to better define the demographics and outcomes of individuals with CF over the age of 40 [Simmonds *et al.* 2010, 2009; Hodson *et al.* 2008; Rodman *et al.* 2005].

It is generally presumed that individuals diagnosed late (as adults) have milder disease markers, less symptoms and therefore a better prognosis. As a result, it has often been hypothesized that the contribution of these individuals to the entire cohort may skew survival data [Rodman *et al.* 2005]. Simmonds and colleagues report a cohort of 112 CF adults >40 years of age who had not undergone transplantation. In this population of survivors, 28% were diagnosed within the first year of life and two thirds of whom were diagnosed prior to age 16, suggesting previous assumptions were not entirely correct [Simmonds *et al.* 2009]. The prevalence of F508del homozygous patients was 30% of the >40 population and individuals who were F508del compound heterozygotes had a 'mild' second mutation in only 25% of instances. Furthermore, patients frequently displayed phenotypes associated with classic CF including pancreatic insufficiency (82%) and chronic airways colonization with *Pseudomonas aeruginosa* (76%). As such, it can be observed that individuals with classic CF still comprise a large portion of those reaching the age of 40. However, improved survival remains a distinctive feature of individuals with CF diagnosed later in life [Rodman *et al.* 2005].

Table 1 includes information on 421 unselected individuals with CF surviving to age 40 from five different treatment centres. It can be observed that these individuals still experience a significant burden of chronic lung disease. Median forced expiratory volume in one second (FEV_1) of this cohort at age 40 approximates 50% (interquartile range [IQR] 28–73) and remains relatively stable until age 55 decreasing at –0.4%/year [Hodson *et al.* 2008]. Chronic airway infection with CF pathogens remains common, but is variable depending on the reporting centre. Patients are chronically infected with *P. aeruginosa* (46.7–77.8%), *Staphylococcus aureus* (20.7–61.1%), *Haemophilus influenzae* (0–22.2%), *Burkholderia cepacia* complex (1.7–22.7%) and *Stenotrophomonas maltophilia* (1.1–22.2%). However, the requirement for hospitalization and treatment with parenteral antibiotics for a pulmonary exacerbation event remains

Table 1. Demographic features of individuals with CF >40 years of age from published cohorts [Hodson *et al.* 2008; Rodman *et al.* 2005].

Category	L	M	T	V	D*	Total
Defining features						
Population size	115	89	115	47	55	421
Female *n* (%)	48 (42)	31 (35)	47 (41)	21 (45)	30 (55)	177 (42)
Paediatric diagnosis *n* (%)	83 (72)	53 (60)	71 (62)	15 (37)	28 (51)	250 (59)
Pancreatic insufficient	96 (84)	70 (79)	65 (57)	19 (40)	26 (47)	276 (66)
F508del/F508del	41 (43)	35 (45)	28 (26)	4 (9)	11 (20)	119 (28)
F508del/other	51 (53)	34 (44)	55 (52)	23 (50)	22 (40)	185 (44)
Outcomes at age 40						
Median FEV_1		52**			49	52
Median BMI		23**			N/A	23
Chronic *Pseudomonas aeruginosa*	89 (78)	63 (71)	54 (47)	26 (56)	42 (77)	274 (65)
CFRD	32 (28)	19 (21)	39 (35)	10 (21)	16 (29)	116 (28)
CFLD – portal hypertension	5 (4.3)	0 (0)	9 (8)	0 (0)	N/A	14 (4)
Lung transplantation	22 (19)	10 (11)	21 (18)	1 (2)	7 (13)	61 (14)

L, London; M, Minnesota; T, Toronto; V, Verona; D, Denver; FEV_1, forced expiratory volume in one second; BMI, body mass index; N/A, not available; CFRD, cystic-fibrosis-related diabetes; CFLD, cystic fibrosis liver disease.
*Composite of early diagnosis and late diagnosis adults >40 years.
**Site-specific data not available.

an infrequent event occurring 0.4 and 0.7 times per annum, respectively, in the 5 years leading to their 40th birthday [Simmonds *et al.* 2009]. Surprisingly, given its association with increased rates of pulmonary function decline, allergic bronchopulmonary aspergillosis affects up to 9–10% of long-term survivors [Simmonds *et al.* 2009; Hodson *et al.* 2008]. Pneumothorax remained an uncommon event affecting 7–11% of individuals >40 years of age. Contrasting other studies where pneumothorax was associated with a poor outcome, mean survival following pneumothorax in this population was 122 months [Simmonds *et al.* 2009; Hodson *et al.* 2008]. Episodes of major hemoptysis had been observed in 11–14% of individuals.

A recent case–control study sought to determine early prognostic markers of longevity based on information available at time of transition from paediatric to adult CF care [Simmonds *et al.* 2010]. They compared a group of patients surviving to >40 years of age ($n = 78$) with a control group matched by year of birth who by the age of 30 had either been transplanted or succumbed to their disease ($n = 152$). Features at transfer from paediatric to adult care associated with long-term survival were later diagnosis (5–16 years of age), a nonrespiratory presentation and increased with increasing height, weight, BMI and baseline pulmonary function. Patients who had died or received transplant were more likely at transfer to have had pneumothoraces, school disruptions owing to illness and received either inhaled or intravenous antibiotics.

As the CF population ages, reanalysis of their demographics is changing traditional predictors of survival. Socioecomonic differences were not noted to be a major factor influencing survival to age 40 in the case–control study of Simmonds and colleagues [Simmonds *et al.* 2010]. This information contrasts studies that demonstrate lower socioeconomic status is associated with advanced airways disease, recurrent pulmonary exacerbations [Schechter *et al.* 2009] and increased mortality [O'Connor *et al.* 2002; Schechter *et al.* 2001]. It is more likely that small sample size and lack of direct means of assessing socioeconomic status underestimated this well-established risk factor for early death. In a cross-sectional database assessment of almost 30,000 individuals with CF, McCormick and colleagues compared outcomes between patients in European Union (EU) countries *versus* non-EU countries to determine the impact of differential healthcare spending [McCormick *et al.* 2010]. In this study a significant increase in the proportion of patients in older age ranges was observed: 18–40 years of age 42% *versus* 26%, respectively, and >40 years of age 5% *versus* 2%. When adjusted to include only those individuals homozygous for F508del no change in parameters were noted suggesting these findings are not due to an increase in the proportion of mild cases diagnosed in the EU. Given the similar prevalence of disease and spectrum of mutations it has been suggested that this difference results from reduced availability of specialists, infrastructure and disease-modifying drugs.

Female CF patients have been noted in many studies to have poorer outcomes relative to their male counterparts [Kulich *et al.* 2003; Fogarty *et al.* 2000] but variable patterns were observed in long-term survivor cohort studies. In a single-centre report, females dominate the older than 40 category [Rodman *et al.* 2005]. This, however, may be due to a referral bias at this centre in which many women were diagnosed late in life on the basis of nontuberculous mycobacterial chronic lung infections.

Individuals surviving to age 40 continue to have long life expectancy in the ensuing years. Of those patients with CF who reach the age of 40, their median survival is 53 years [Hodson *et al.* 2008]. Survival curves remain linear until age 60 with an estimated death rate of 3.4%/year.

Current challenges: nonpulmonary complications occurring in the ageing CF cohort

With the continued improvement in survival of individuals with CF there is an increasing need to focus on extrapulmonary disease comorbidities. As the ageing CF cohort represents a unique demographic of individuals with CF, the constellation of complications that ensue is also different (Figure 1). While no CF-related complication is unique to this older cohort, the relative occurrence of events can be dramatically different. As illustrated above, this group is diverse. It includes individuals diagnosed both early and late, as well as individuals who have received life-saving lung transplantations. Many complications will be shared, whereas other complications may be unique to a particular

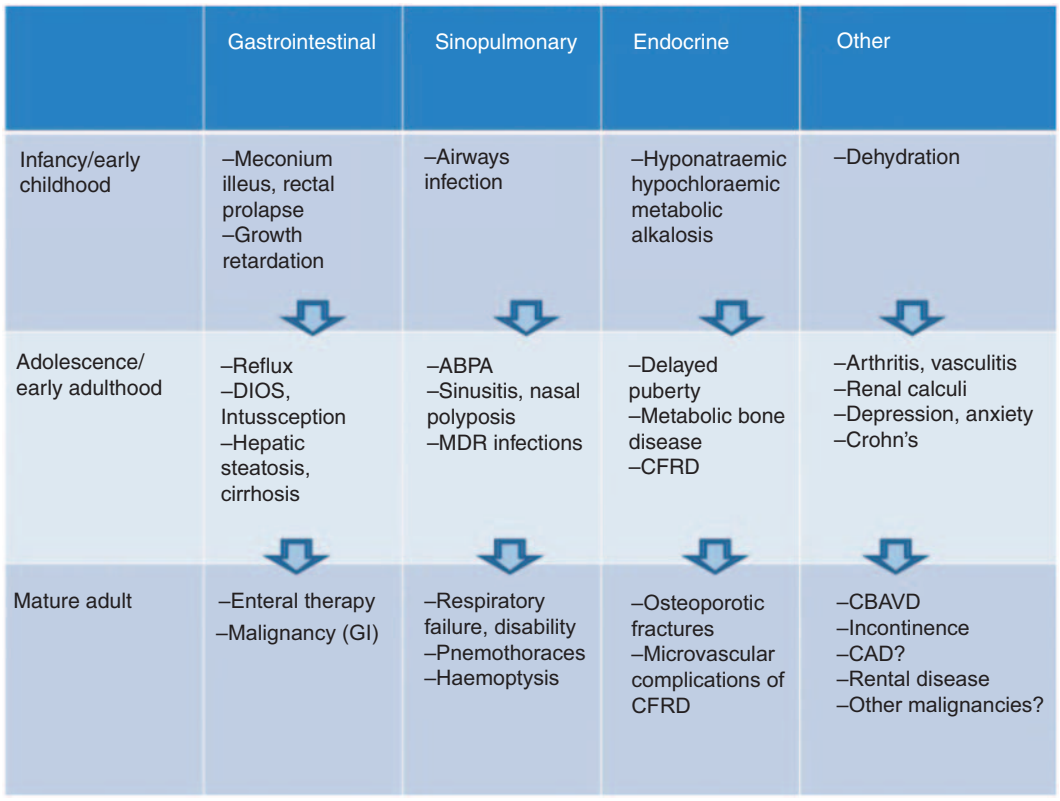

Figure 1. Burden of disease with increasing age in cystic fibrosis. DIOS, distal intestinal obstruction syndrome; ABPA, allergic bronchopulmonary aspergillosis; MDR, multiple-drug-resistant; CFRD, cystic-fibrosis-related diabetes; GI, gastrointestinal; CBAVD, congenital bilateral absence of the vas deferens; CAD, coronary artery disease.

surviving cohort (such as pancreatitis effecting those individuals who are pancreatic sufficient). The long-term complications uniquely associated with lung transplantation are beyond the scope of this manuscript and the reader is referred to several recent quality reviews [Morton and Glanville, 2009; Aratari *et al.* 2008; Meachery *et al.* 2008; Kotloff and Ahya, 2004]. Furthermore, CF patients who have undergone transplantation continue to suffer manifestations of CF in all other native organs.

Psychosocial challenges in the ageing CF cohort

Clinicians are increasingly aware of the distinction between suffering from CF and living with CF. Increasingly, patients are achieving higher levels of social integration owing to improvements in physiological functioning when entering adulthood. Of adults with CF up to 70% are gainfully employed, or pursuing advanced education, whereas only 5–15% are reported as disabled [Cystic Fibrosis Trust, 2008; Canadian Cystic Fibrosis Foundation, 2007]. Marriage is now a common prospect for individuals with CF and 32–42% of adults on CF registries are married [Cystic Fibrosis in Australia, 2008; Canadian Cystic Fibrosis Foundation, 2007]. With the assistance of medical technology CF patients are increasingly becoming parents. The development of sperm aspiration techniques, and intracytoplasmic sperm injection has enabled men who had previously been considered infertile owing to congenital bilateral absence of the vas deferens to father children. Outcomes of women with CF pursuing pregnancy have dramatically improved and, although associated with increased short-term medical needs and complications, does not seem to confer long-term survival disadvantage [Goss *et al.* 2003; Johannesson, 2002; Gilljam *et al.* 2000]. As a consequence, the number of women pursuing pregnancy has increased fourfold from 1986 to 2004 [Sueblinvong and Whittaker, 2007]. However, despite these successes, individuals with CF and their partners pursuing pregnancy must accept the very real possibility that their child will prematurely lose a parent.

Those same medical regimens credited with improving life spans are unfortunately, costly, laborious and time consuming, consequently limiting quality of life. A recent survey of 204 patients attending 10 different centres conducted by Sawicki and colleagues found that the mean daily time dedicated to CF treatment regimens was 108 minutes [Sawicki *et al.* 2009]. Such burdens pose tremendous challenges to patient self-management strategies, in particular in those adults trying to balance family life, careers/education, and other responsibilities with management of their CF. New treatments and modalities will need be mindful of further contributing to patient treatment burden as these are typically supplementary measures rather then replacement therapies. As such, the pursuit of dry powder inhalers and high efficiency nebulization devices for use of established and new aerosolized antimicrobials and mucolytics is encouraging.

Clinicians are increasingly aware of the impact of chronic medical conditions on psychological health. The prevalence of both depression and anxiety have (variably) been shown to be increased in CF adults relative to the general population at approximately 30% [Riekert *et al.* 2007; Pearson *et al.* 1991]. As both anxiety and depression have been shown to vary with increasing burden of lung disease it would be expected that these conditions will increasingly be observed in the ageing adult cohort. The expected increase in psychosocial needs of the ageing CF cohort will not be met with existing clinic staffing in social work or psychology. As such, the psychosocial impact of ageing in CF remains an area which requires significant study in order to identify new and emerging needs and develop the infrastructure and expertise to meet these needs.

Pancreatitis

Pancreatitis is a recognized complication of adults with CF and in many instances a presenting complaint in those diagnosed late in life. In classical CF, pancreatic ductal secretions of enzyme-rich material are blocked by inspissated mucins owing to defective CFTR function and result in the autodigestion of the pancreas from retained secretions. In the vast majority, pancreatic insufficiency manifests in infancy and is readily diagnosed. However, in those individuals with milder mutations resulting in a partially active CFTR (class IV or V) secretions are semiviscid resulting in maintenance of pancreatic sufficiency but potentially punctuated by episodes of intermittent ductal obstruction manifesting as pancreatitis [Walkowiak *et al.* 2008].

For an individual to develop pancreatitis they must have a residual portion of normal pancreatic acinar tissue. Exocrine pancreatic sufficiency can continue to be displayed in individuals until almost 98% of reserve function has been lost. Pancreatitis occurs only in those CF individuals with at least partial pancreatic sufficiency [Augarten *et al.* 2008]. It is estimated that only 10.2–19% of individuals with CF retain pancreatic sufficiency [Dray *et al.* 2003; Durno *et al.* 2002; Gaskin *et al.* 1982]. The incidence of pancreatitis varies from 1.2–4.0% in the overall CF population [Augarten *et al.* 2008; De Boeck *et al.* 2005; Durno *et al.* 2002]. However, in individuals who retain exocrine pancreatic function its incidence ranges from 10.3–14.2%. These individuals are characterized by an older age (mean 24.4 years), milder genetic mutations, and usually a milder course of respiratory disease [De Boeck *et al.* 2005; Gaskin *et al.* 1982]. Furthermore, both a chronic low-grade inflammatory process punctuated by acute episodes of pancreatitis contribute to the destruction of residual pancreatic acinar tissue which can convert pancreatic sufficient to pancreatic insufficient status later in life [Durno *et al.* 2002]. In one study, 45% of individuals with CF and pancreatitis were >35 years of age [Krysa and Steger, 2007].

CF-related diabetes

While CF-related diabetes (CFRD) shares features with both type I and II diabetes mellitus it represents a unique clinical entity and requires a distinct management strategy. The disease is characterized by a progressive fibrotic disruption and fatty infiltration of pancreatic microarchitecture resulting in a loss of islet cells and an increasing insulin deficiency. Increased peripheral insulin resistance has also been suggested, but recent data suggests this may not play as significant a role as lack of insulin [Mohan *et al.* 2009; Dobson *et al.* 2004]. However, ketoacidosis is extremely rare in CFRD. The spectrum of disease ranges from impaired glucose intolerance to CFRD with or without fasting hyperglycaemia. To add further complexity, an individual's glucose tolerance and insulin resistance remain plastic and fluctuate with periods of infection/inflammation and

gastrointestinal absorption and motility. Most patients with CFRD without fasting hyperglycaemia will progress with time to develop fasting hyperglycaemia [Schwarzenberg *et al.* 2007].

CFRD has an overall reported prevalence of 11–21.5% [Cystic Fibrosis Foundation, 2008; Cystic Fibrosis Trust, 2008] depending on regional database. While less well documented, IGT prevalence in CF has been documented in smaller centre-specific cohort studies to be 13.7–16% [van den Berg *et al.* 2009; Schwartz *et al.* 1992]. Although numerous risk factors have been associated with CFRD, increasing age is most notable. Prevalence increases from 2–3% in those aged 6–10 to 5–10% in those aged 11–17 to 13.5–17.5% in young adults 18-24 years of age [Cystic Fibrosis Foundation, 2008; Canadian Cystic Fibrosis Foundation, 2007]. In those CF adults over the age of 40 its prevalence in studies ranges from 27–52% [Simmonds *et al.* 2009; van den Berg *et al.* 2009; Hodson *et al.* 2008]. Not only does CFRD exist more frequently in the adult cohort of CF patients but it also develops more frequently in adults. In a population based longitudinal study using data from UK CF Registry, Adler and colleagues followed 5196 individuals with CF without CFRD to determine the incidence of CFRD from 1996–2005 [Adler *et al.* 2008]. The incidence of CFRD was observed to increase with increasing age up to the fourth decade of life at (7.2% for females, 6.5% for males) before again declining. Other independent variables associated with the development of CFRD in decreasing order included declining pulmonary function, pancreatic insufficiency, CFTR class (I and II *versus* others), female sex, liver disease and corticosteroid use.

The development of CFRD has been associated with increased rate of pulmonary function decline and increased rates of pulmonary exacerbations [Koch *et al.* 2001]. It is also a marker of poorer nutritional status and an independent predictor of mortality [Chamnan *et al.* 2010; Marshall *et al.* 2005; Koch *et al.* 2001; Rosenecker *et al.* 2001; Milla *et al.* 2000]. The diagnosis and correct management of CFRD can correct the pulmonary function decline in CF, confirming that CFRD independently contributes to disease progression and is not merely a marker of advanced disease [Lanng *et al.* 1994]. As such, the characterization of a patient's glucose tolerance is critical. In addition to currently recommended annual screens (with 75 g oral glucose tolerance tests) and symptom directed monitoring (polydipsia/polyuria, growth failure, weight loss, otherwise unexplained pulmonary function decline), centres are increasingly observing for postenteral nutrition hyperglycaemia or exacerbation-induced postprandial hyperglycaemia.

Microvascular complications of CFRD are more common in individuals with CFRD with fasting hyperglycaemia, CFRD of longer duration and with poorer control of disease [Schwarzenberg *et al.* 2007]. The prevalence of diabetic retinopathy ranges from 10% to 27% [van den Berg *et al.* 2008; Schwarzenberg *et al.* 2007; Andersen *et al.* 2006]. Neuropathy has been reported to be present in up to 42% of individuals, with autonomic abnormalities detected in 34% and somatic abnormalities in 17% [Schwarzenberg *et al.* 2007]. Microalbuminuria as a manifestation of diabetic nephropathy is a common in individual with CFRD with a prevalence of 13–21% [van den Berg *et al.* 2008; Schwarzenberg *et al.* 2007; Andersen *et al.* 2006]. Furthermore, concomitant CFRD even in the absence of nephropathy is likely to predispose individuals to antibiotic-induced acute kidney injury, an increasingly commonly recognized event [Etherington *et al.* 2007]. As microvascular complications associated with CFRD accumulate with time, their presence will increasingly be observed in the ageing CF cohort. Whereas there is significant evidence in the type 1 and type 2 literature that strict glycaemic control reduces microvascular complications, the same has not yet been documented for CFRD. It is hoped that by achieving glycaemic targets, CF patients can not only enjoy improved pulmonary health but also fewer diabetic complications. To this end, it is vital that all patients with CFRD be screened yearly for retinopathy, nephropathy and neuropathy.

Metabolic bone disease in cystic fibrosis

Metabolic bone disease is common in CF. Osteoporosis is characterized by low bone mass, poor bone quality with a consequent increase in risk of bone fragility and fracture. In CF, this process is multifactorial. The pathogenesis relates in part to the gastrointestinal complications of CF: malnutrition, insufficient absorption of vitamins D and K (primarily owing to pancreatic insufficiency) and impaired absorption/excess secretion of calcium from the gastrointestinal tract altogether resulting in a low BMI. It also

is affected by pulmonary factors: physical inactivity owing to burden of disease and chronic infection/inflammation cause increased cytokine activity. There are also hormonal factors: low levels of insulin-like growth factor 1 (IGF-1) and delayed puberty/hypogonadism. Finally, complications of medical management including the use of corticosteroids play a large role [Aris *et al.* 2005]. As a consequence of these events adolescents with CF often fail to reach peak bone mass and furthermore all individuals with CF suffer accelerated bone losses [Lutz, 2001; Bhudhikanok *et al.* 1998]. Dual-energy X-ray absorptiometry (DXA) represents the current gold standard for bone mineral density (BMD) measurement and is performed at the lumbar spine (L2–4), femoral neck and total hip. Via this measurement osteoporosis is defined as a T score of <-2.5 (relative to a gender-matched young population) and osteopenia as between -1 and -2.5.

Increased rates of fractures of long bones, ribs, and vertebrae have all been reported in CF. Not only are fractures associated with significant pain and suffering but they can also contribute to worsening pulmonary disease status. Acute fractures of ribs and vertebrae can significantly impair chest physiotherapy regimens and contribute to pulmonary exacerbation [Aris *et al.* 2005]. Furthermore, exaggerated kyphosis owing to loss of vertebral body height with repeated fractures can also introduce a restrictive lung disease element [Aris *et al.* 1998; Logvinoff *et al.* 1984].

A recent meta-analysis of 10 studies involving 888 patients assessing bone disease in CF patients, Paccou and colleagues estimated the pooled prevalence of osteoporosis in the adult CF population of 23.5% (CI 16.6–31.0) [Paccou *et al.* 2010]. The pooled prevalence of osteopenia was 38% (CI 28.2–48.3). Pooled prevalence of vertebral and other fractures were 14% (CI 7.8–21.7) and 19.7% (CI 6–38.8). Vertebral fractures occur almost exclusively in thoracic vertebrae. This fracture rate exceeds that of age-matched healthy controls by a factor of 100 and that of untreated postmenopausal osteoporotic women [Aris *et al.* 2005; Liberman *et al.* 1995]. Interestingly, the presence of fractures paradoxically decreases with increasing age likely reflecting a survivor bias.

Strides in the management of CF-related metabolic bone disease continue to be made. First and foremost, the early recognition of risk and enhanced surveillance for metabolic bone disease following published guidelines is required [Aris *et al.* 2005]. Management strategies using calcium, vitamin D and K supplementation, sex hormone therapy, and antiresorptive agents are implemented as individual circumstances dictate. Although stabilizing BMD can be achieved, prevention of bone disease through the improved pulmonary and nutritional management strategies holds greater promise. To this end, the foundation for a lifetime of bone health begins in childhood and is dependent upon nutrition, adequate weight gain and physical activity. This will allow the appropriate hormonal milieu in which to accrue normal bone mass as a child and not to have accelerated bone loss as an adult. For the ageing CF patient, the future will hold treatment for bone disease at both a frequency and chronologic age similar to the general population.

Urinary incontinence

Stress incontinence is a frequent and underreported condition commonly affecting women with CF, and is often only divulged after direct questioning. Defined as an involuntary leakage of urine, stress incontinence symptoms are exacerbated in CF during spells of coughing or during physiotherapy. Symptoms are more severe during pulmonary exacerbations and may impede performance of effective chest physiotherapy [Nixon *et al.* 2002]. Prevalence estimates vary from 30% to 74% in different cohorts [Vella *et al.* 2009; Moran *et al.* 2003; Cornacchia *et al.* 2001]. Prevalence increases with increasing age [Vella *et al.* 2009; Cornacchia *et al.* 2001] and decreasing FEV_1 [Cornacchia *et al.* 2001]. In those CF females over 35 years of age, the prevalence is 80–100% [Orr *et al.* 2001]. Proper identification of patients can enable teaching of pelvic floor muscle exercises, which can reduce symptoms and improve quality of life.

Malignancies in CF

An association between malignancies and CF was first proposed in the 1980s when several independent cases were reported. Since then, several epidemiologic investigations have sought to further elucidate this association. These studies use standardized incidence ratios (SIRs), the ratio of observed compared with the ratio of expected cancers in a cohort extrapolated from general population data, as a measure of relative risk.

A clear and consistent increase in the risk of gastrointestinal and pancreatic malignancies has since been established. Gastrointestinal malignancies have been found to occur at SIRs 5.1–6.5 times that of the general population [Johannesson *et al.* 2009; Maisonneuve *et al.* 2003; Schoni *et al.* 1996]. In particular, cancer diagnoses involving the small intestine (SIR 24.8), colon (SIR 7.4), biliary tract (SIR 39), liver (SIR 4.1), oesophagus (SIR 5.4) and pancreas (SIR 2.6–5.3–31.5) are increased in CF [Maisonneuve *et al.* 2007, 2003; Neglia *et al.* 1995]. The mechanism of the increased risk of gastrointestinal malignancies has not been established. This risk can be observed to increase with increasing age in the CF cohort [Maisonneuve *et al.* 2003]. Furthermore, the frequent and varied gastrointestinal complaints common in CF (distal intestinal obstruction syndrome, fibrosing colonopathy, rectal prolapse, etc.) may delay the diagnosis of more ominous causes of gastrointestinal disturbances [Brown *et al.* 2000]. Not only do CF patients have an increased risk of developing malignancy, they manifest disease at an earlier age. CF patients developed gastrointestinal malignancies at a mean age of 32.2 years (±12.6) compared with 58.2 years (±14.3) in the general White population [Neglia *et al.* 1995].

There are, however, conflicting data as to whether CF confers an increased risk of all types of cancer [Johannesson *et al.* 2009; Maisonneuve *et al.* 2003; Schoni *et al.* 1996; Neglia *et al.* 1995, 1991; Sheldon *et al.* 1993]. In the largest of these studies Nelgia and colleagues using a retrospective cohort study assessed malignancy risk independently in both North American and European CF populations comprising more than 38,000 individuals and did not detect an increased risk of cancer [Neglia *et al.* 1995]. More recently, Johannesson and colleagues, using a retrospective general population-based study using multiple Swedish National Registries, reported on 883 CF patients followed from 1968 to 2003 where they observed an increased risk of any cancer of 3.2 (CI 2.1–4.6) [Johannesson *et al.* 2009]. In addition to reaffirming the increased incidences of gastrointestinal and pancreatic malignancies in CF, these investigators also observed increased incidences of thyroid and renal cancers, nonmelanoma skin cancers and lymphoma. The increased incidences of these malignancies, all of which are increased with radiation exposure could be explained by the repeated exposure of CF patients to radiographic imaging studies at an early age. Accordingly, the routine use of computed tomography (CT) for monitoring lung disease in CF needs to be followed with great care for future implications [de Gonzalez *et al.* 2007].

Investigators have sought to identify particular risk factors associated with malignancy in CF [Maisonneuve *et al.* 2003; Neglia *et al.* 1995]. Genotype does appear to have an impact on the risk of gastrointestinal malignancies as individuals who are homozygous for the F508del mutation had the highest risk, intermediate risk for F508del compound heterozygotes and lowest for individuals with other mutations [Maisonneuve *et al.* 2003]. This is interesting as there is no increased incidence of malignancies in family members of individuals with CF [Johannesson *et al.* 2009]. Individuals whose diagnosis was made on the basis of failure to thrive were also noted to be at increased risk of gastrointestinal malignancies [Maisonneuve *et al.* 2003]. CF lung transplant recipients have an increased risk of cancer over all (SIR 6.3; CI 3.4–10.8) and specifically an elevated risk of gastrointestinal malignancy (SIR 21; CI 5.8–54.2) and lymphoma (SIR 43.8; CI 17.7–90.7). These have largely been attributed to the intense immune suppressive regimen required [Maisonneuve *et al.* 2003].

Despite the clear and consistent increased risk of gastrointestinal malignancies in CF, individual risk remains very low. However, as the life span of individuals with CF continues to increase, the absolute risk of malignancies is expected to increase. There are no recommendations for enhanced surveillance for cancer in patients with CF. Screening should be considered on an individual basis after a thorough evaluation of one's symptoms, perceived risk factors and the risk of the required procedure.

Future challenges

With improved survival comes new challenges for the CF patient. Just as improved survival into the middle adult years has brought with it an array of complications, one might expect a whole new array of clinical problems to occur as more patients reach their fifth and even sixth decade of life. Several candidate problems have already emerged.

Macrovascular disease

To date, coronary artery disease (CAD) has only rarely been reported in CF individuals outside of the posttransplant setting [Onady and Farinet, 2006; Fraser *et al.* 1999; Schlesinger, 1997]. Indeed, the favourable blood pressure and lipid profiles of patients with CF [Rhodes *et al.* 2010; Figueroa *et al.* 2002], combined with increased mortality at a younger age have long been suggested to protect this population from CAD. Recently, Hull and colleagues compared the arterial stiffness of 50 adult CF patients (mean age 28 ± 8.2 years) with age-, sex- and BMI-matched controls [Hull *et al.* 2009]. After adjustment for confounders, augmentation index (AIx; a composite vascular endpoint comprising both arterial stiffness and global peripheral wave reflection) was observed to be significantly elevated in individuals with CF and increase with age. In particular, those individuals with concomitant CF-related diabetes had the highest AIx. Increased arterial stiffening is a hallmark of the ageing process, and an independent predictor of atherosclerotic CAD evident even in those without obvious risk factors for CAD [Laurent *et al.* 2006]. These findings suggest that premature vascular ageing occurs in CF, as the large artery haemodynamics of individuals with CF were behaving approximately a decade in advance of those expected for their chronologic age. Whether this is related to CF itself or a complication of its treatment is unknown. Importantly, family history is a well-documented risk factor for both early CAD and dyslipidaemia. As CF patients age, this genetic background will figure more prominently in the development of CAD. Thus, it is possible that an increase in the incidence of symptomatic CAD will occur in CF.

Iatrogenic complications of medical management

The cumulative effects of therapies need be considered as well. Acute kidney injury as a result of nephrotoxic antibiotics such as aminoglycosides and polymixins are increasingly being reported [Smyth *et al.* 2008; Al-Aloul *et al.* 2005b]. Furthermore, evidence suggests that repeated exposure to nephrotoxic antimicrobials may result in cumulative subclinical renal injury with the potential to manifest later in life with overt chronic renal disease [Etherington *et al.* 2007]. In a prospective cohort study by Al-Aloul and colleagues reduced renal function as measured by 24-hour urine creatinine clearance (CCL) in a cohort of 80 patients chronically infected with *P. aeruginosa* was observed in up to 42% of individuals with a CCL of <80 ml/min/1.73 m^2 and 21%L with a CCL of <60 ml/min/1.73 m^2 [Al-Aloul *et al.* 2005a]. As glomerular filtration decreases with increasing age, it is possible that in the ageing CF cohort renal complications will increasingly occur with standard exacerbation therapies. In a similar fashion neuropathies (secondary to linezolid [Bressler *et al.* 2004; Frippiat and Derue, 2004], chloramphenicol [Godel *et al.* 1980] and oto-vestibular toxicities with aminoglycosides [Cheng *et al.* 2009; McRorie *et al.* 1989]) may ensue.

Conclusions

In the last decade the number of adults with CF has now surpassed the number of children with CF owing to improved therapies. Using large national and international registries we can see that increasing numbers of patients are entering their fourth and fifth decade of life. While encouraging in and of itself, studying this cohort of patients may hold promise for other patients. In analysing the demographics of patients who survive disproportionately longer, healthcare providers can identify those areas to maximize therapeutic interventions to further improve survival in younger cohorts of patients.

The importance of high-quality paediatric care in setting the stage for a long and healthy life with CF is evident. In studies of long-term survivors it has been clearly demonstrated that those individuals transferring to adult care who have remained infection free, and achieved optimal growth and preserved lung function are much more likely to survive to age 40 [Simmonds *et al.* 2010]. The practice of early eradication therapy during the initial phases of *P. aeruginosa* colonization and infection is a particularly relevant intervention only recently being widely adopted [Ratjen *et al.* 2010; Langton Hewer and Smyth, 2009]. Furthermore, the potential long-term impact of therapies and medical interventions in early life on complications that occur later in life need be considered at all stages of disease. This is especially true for those individuals who undergo transplantation.

As the survival of patients with CF continues to improve it is vital that CF healthcare providers adapt to meet both existing and emerging needs of this population. The demographics of this patient population are unique and as such the

constellation of complications experienced is similarly distinct. Recognizing the potential for these complications in this population is integral in the provision of life-long medical care. Observation, and screening as required, can detect early manifestations of complications and limit their subsequent impact.

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Conflict of interest statement

None of the authors have competing interests to declare.

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