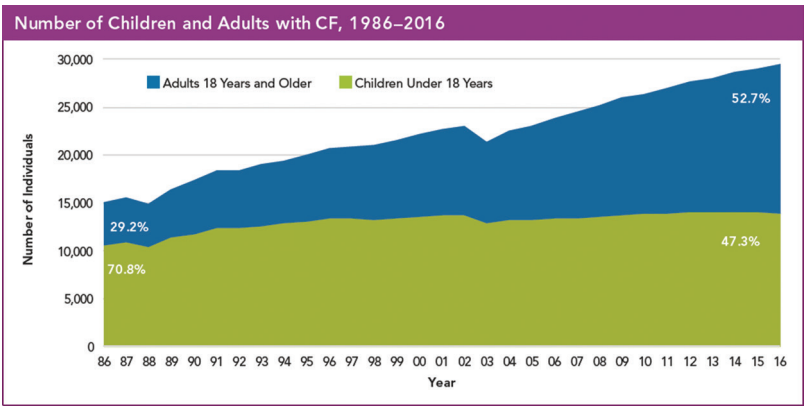
16. Aging in cystic fibrosis

Authors: Dagmar Lin, Thomas Geiser

1. INTRODUCTION

- Currently, 70.000 people are affected by CF globally, over 30.000 from North America and Europe. Survival of CF patients has improved significantly over the last decades as a result of an improved understanding of the mechanisms and the natural course of the disease. This led to more efficient airway clearance techniques, nutritional support and key medications. Multidisciplinary care in dedicated CF centers addressing the pulmonary, extra-pulmonary and psychosocial aspects of CF contributed significantly to the improvement of patient outcomes.
- Nowadays, the majority of CF patients reach adulthood and more than 50% of the USA, Canadian and Western European CF population is above 18 years of age. The number of adult patients has been increasing steadily during the last decades **(Figure 1)**.
  - Transition has become an inevitable process in CF care.
  - With increasing age, the severity of lung disease also increases, pulmonary complications may develop and multi-resistant bacteria become more prevalent.
  - Prolonged survival exposes CF patients to extra-pulmonary diseases, some of which were rarely encountered in the past.
- It is essential to diagnose these comorbidities and complications as early as possible and provide appropriate care to prolong survival and optimize quality of life (QoL).
- This chapter summarizes the main challenges associated with the aging of the CF population. For more details on each of the following points, please see the corresponding chapters.

Figure 1: Proportion of adult and pediatric patients overtime (reprinted with permission from the Cystic Fibrosis Foundation, 2016 Patient Registry Annual Data Report[1])



Note: the decrease in the number of individuals in 2003 is due to a delay in obtaining informed consent forms before the close of the calendar year at some CF care centers

2. CHALLENGES OF TRANSITION

- Given the increasing survival of CF patients, **a formalized transition process is necessary to ensure continuity of care.** Every transition process needs to be timed well and accustomed to the adolescent's chronological age and physical and cognitive maturity.
- Success of recommendations for more gradual, developmentally appropriate procedures involving all members of the CF team depends on **clear and active communication** between pediatric and adult care teams, parents, and adolescents.

2.1 Adherence

- Suboptimal adherence to medical advice and treatment is well documented in chronic illnesses in general.
- Treatment of an adult CF patient involves a median of 7 different medications (reported range 0-20). Treatment administration and physical therapies take on average 2-3 hours per day of the patient's time.
- Consequences of suboptimal adherence include increased symptoms, accelerated decline of lung function, more frequent hospitalizations, increased family stress and conflict, and higher health care costs.
- Minor symptoms and the feeling or appearance of well-being create the false sense that the disease is not active and therefore reduces the motivation to adhere to the required daily care. Moreover, in contrast to symptomatic treatments, therapy aiming at the prevention of complications is not associated with the direct perception of its efficacy and this can contribute to poor adherence.

2.2 Partnership and parenthood

- Parents with CF are now more common in all adult CF centers.
- Pregnancy requires careful interdisciplinary care and close teamwork between the obstetric and CF teams. While medium-term outcomes (<10 years) do not appear to be adversely affected by pregnancy and motherhood, the impact on daily self-management can be challenging for the patients.
- Obstructive azoospermia due to the absence of vas deferens results in infertility in 98% of male CF patients. Nowadays, various methods of reproductive medicine allow CF patients to become parents. Interdisciplinary counseling is crucial in this regard.

2.3 Higher education and employment

- Approximately one-third of all adults are in full-time employment, but there is variation in the proportion of patients who report being in part-time work or unemployment and receiving some form of disability support.
- Loss of employment or long-term unemployment is associated with poorer health.
- Important work-related issues include decision to disclose diagnosis of CF and guidance on employment or vocational training decisions.

3. PULMONARY MANIFESTATIONS IN THE AGING CF POPULATION

- The severity of pulmonary disease increases with age **(Figure 2)**, and although, the proportion of patients having FEV_1<40% has decreased over the years, respiratory insufficiency remains the main cause of mortality in CF.

- Complications such as pneumothorax, hemoptysis, and pulmonary hypertension may develop and are associated with increased morbidity and mortality.
- Lung transplantation is the ultimate therapy option for CF patients with end-stage lung disease and, in well-selected candidates, it can provide a survival benefit and improve QoL. Age at transplantation is increasing in CF. However, not all adults with end-stage CF lung disease ultimately opt for lung transplantation.
- The prevalence of bacteria changes overtime, and *P. aeruginosa* and other multidrug-resistant microorganisms become more prevalent with age **(Figure 3)**. In the time of antibiotic stewardship, there is more awareness of the role of antibiotic exposure on the development of antimicrobial resistance. Increasing antibiotic resistance renders treatment of CF infections challenging.

Figure 2: FEV_1 change by age (reprinted with permission from the Cystic Fibrosis Foundation, 2016 Patient Registry Annual Data Report[1])

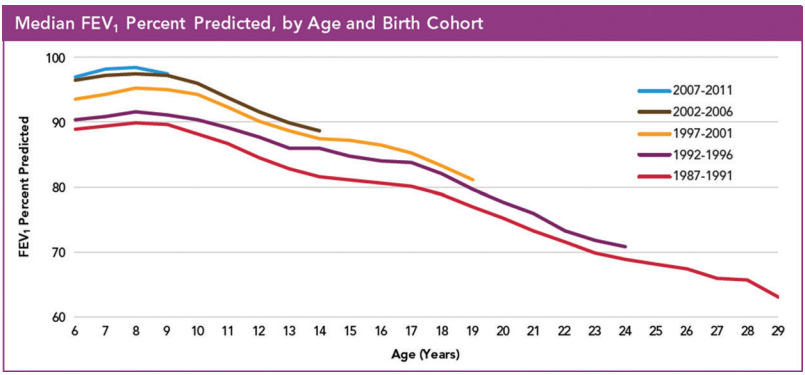
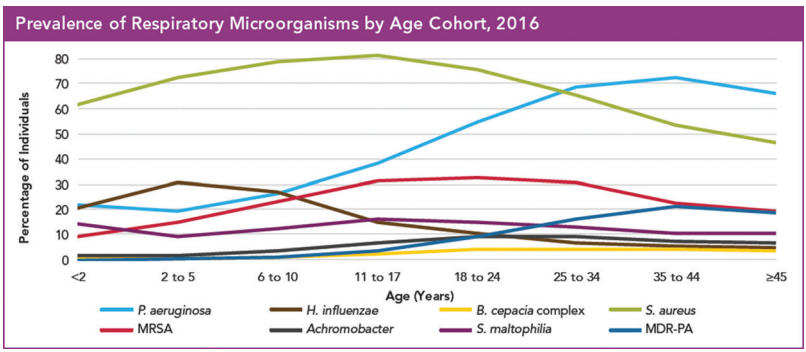


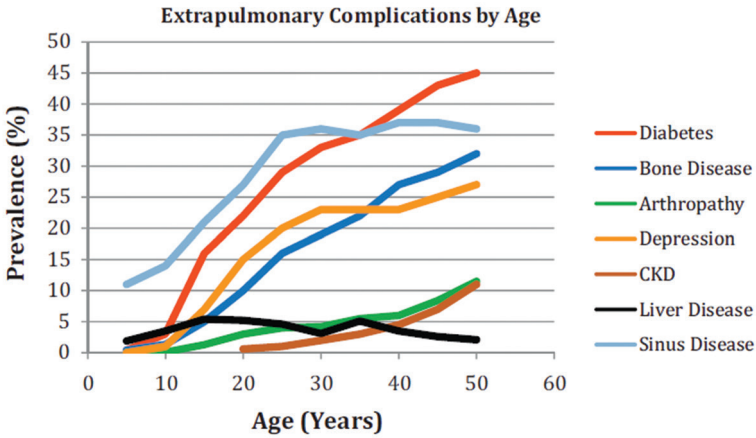
Figure 3: Prevalence of bacteria by age (reprinted with permission from the Cystic Fibrosis Foundation, 2016 Patient Registry Annual Data Report[1])



4. EXTRA-PULMONARY MANIFESTATIONS IN THE AGING CF POPULATION

- CF causes a wide range of extra-pulmonary manifestations and prolonged survival increases their prevalence. Some manifestations were rarely encountered in the past due to the short life span of patients, the majority of whom died during childhood.
- In the following section, we summarize extra-pulmonary sequelae that may occur in CF, with increasing age. **Figure 4** shows examples of extra-pulmonary complications and their prevalence by age.

Figure 4: Examples of CF extra-pulmonary complications by age [reprinted from Quon BS, Moira LA. Paediatric Respiratory Reviews 2012;13(4):206-214[2] with permission from Elsevier Ltd®].



4.1 ENT manifestations

- Chronic rhinosinusitis with or without polyposis, is the most common ENT manifestation in adult CF patients with a prevalence approaching 100% based on imaging criteria.
- Microorganisms present in the lung usually colonize the sinuses too. The sinuses act as a reservoir for these microorganisms maintaining lung infection. As in the case of pulmonary colonization, multidrug-resistant microorganisms become more prevalent with age.
- The risk for drug induced ototoxicity increases with increasing exposure to ototoxic drugs, notably aminoglycosides.

4.2 CF-related diabetes (CFRD)

- **Early diagnosis is essential for the longitudinal management of CF patients due to the association of CFRD with increased morbidity and mortality.** CFRD is an independent predictor of poor pulmonary function, poor nutritional status, increased frequency of hospitalizations and mortality, the latter with a relative risk of up to six-fold greater than in non-CFRD patients.

- The prevalence of CFRD increases with age and is higher in adult female patients. It occurs in approximately
  - 30% of CF patients aged 18 years and older
  - >50% of CF patients aged 50 years and older
- Risk factors for CFRD are summarized in **Table 2 of Chapter *"CF-related diabetes".***
- The prevalence of long-term complications depends on the duration of diabetes and the level of glycemic control.
  - Microvascular complications: In patients with CFRD duration of ≥10 years, nephropathy has been reported in 14% of patients, retinopathy in 16% and autonomic neuropathy in 52% .
  - Macrovascular complications (cardiovascular and cerebrovascular disease) are very uncommon in CF, however, as life expectancy increases, they may become more prevalent.

4.3 Pancreatic insufficiency

- Exocrine pancreatic insufficiency is characterized by the progressive loss of pancreatic parenchyma. Overt pancreatic insufficiency will not appear until more than 90% of pancreatic function is lost.
- Almost 85% of CF patients will be affected by pancreatic insufficiency at some point in their lifetime.
- Pancreatic insufficiency status is strongly associated with the CF genotype and leads to malabsorption requiring pancreatic enzyme replacement therapy (PERT) and replacement of fat soluble vitamins.

4.4 Gastro-esophageal reflux disease (GERD)

- Prevalence is estimated to be between 35 and 81% in children and adults.
- Although it is considered that GERD may contribute to the decline of lung function, its role regarding outcomes in CF is not clear.

4.5 Distal intestinal obstruction syndrome (DIOS)

- DIOS is a complete or incomplete obstruction of the terminal ileum/cecum and proximal colon with viscid feces. It can be difficult to distinguish from constipation.
- It occurs in <10% of children and its prevalence increases in adults to 15%.
- **Table 2 of Chapter *"Intestinal obstructive disorders"*** summarizes risk factors of DIOS.

4.6 CF-related bone disease

- The prevalence of osteoporosis and osteopenia in CF is difficult to establish (mostly due to differences in the definition of osteoporosis/osteopenia in different age groups) but it increases with age, lung disease severity, low body mass index (BMI) and malnutrition.
- **Table 1 of the chapter *"Bone disease"*** summarizes risk factors of low bone mineral density in CF.

4.7 CF arthropathy

- Arthritis is relatively infrequent complication in CF but its prevalence increases with age.
- CF-related arthropathy (CFA) is more common than hypertrophic osteoarthropathy (HOA) (9% vs 7%) with an earlier age of onset (15 vs 20 years).

4.8 Cardiac disease

- Primary heart disease is not a typical feature of CF, but
  - Pulmonary hypertension can develop secondary to hypoxic vasoconstriction and pulmonary vascular remodeling from severe bronchiectasis (prevalence unknown).
  - Coronary artery disease, although uncommon in CF, may become more prevalent as life expectancy increases, especially in patients with other cardiovascular risk factors such as CFRD, arterial hypertension and hyperlipidemia.

4.9 Kidney disease

- Primary renal disease is not a typical feature of CF but
  - CF patients are at risk of developing secondary renal disease, as a result of medication-associated nephrotoxicity and/or CF related diabetes (CFRD).
  - CF has been associated with nephrolithiasis and nephrocalcinosis.
- Renal impairment is more frequent after lung transplantation due to immunosuppressive drugs, such as calcineurin inhibitors, but also drug-induced diabetes mellitus and hypertension.
- Risk factors for chronic kidney disease in CF are summarized in **Table S2 of the Chapter *"Renal disease".***

4.10 Urogenital manifestations

- Stress urinary incontinence is under-reported in CF. Prevalence varies between 30 and 68% in females and 2.2-16% in males.
- Prevalence of incontinence increases with age and worsening lung function.

4.11 Drug allergies and toxic effects

- With increasing age and increasing cumulative antibiotic exposure, prevalence of allergies and drug-induced toxic effects also increases, leading to therapeutic dilemmas making treatment choices challenging.
- Notably, use of systemic aminoglycosides can result in kidney injury and/or otovestibular side effects. Strategies to minimize the toxic effects of aminoglycosides are a major area of focus in CF research.

4.12 Cancer

- In non-transplanted adult CF patients the prevalence of histologically proven malignancy is about 1%.
  - CF patients are at increased risk of gastro-intestinal malignancies (about 5-fold higher risk compared to the general population, median age of diagnosis 39 years) and notably

gastroesophageal, colonic and small intestine. Case report evidence suggests also an association of CF with biliary (cholangiocarcinoma) and pancreatic cancer. The prevalence of non-GI malignancies is similar to the general population.
    - The contributing factors for the increased risk of GI malignancies in CF are not elucidated. It has been hypothesized that repeated imaging studies and exposure to radiation over the years, chronic inflammation and the composition of gut microbiota may play a role.
    - **According to the U.S. CF Foundation, in non-transplanted CF patients, screening for colonic cancer with colonoscopy is recommended from the age of 40. Continued rescreening is recommended every 5 years, unless a shorter interval is indicated by the findings of the most recent colonoscopy.**
      Note: To allow optimal examination during colonoscopy, the U.S. CF Foundation recommends intensive regimens for bowel preparation (such as 3-4 washes with a minimum of 1L purgative per wash and the last wash occurring within 4-6h before the examination).
- After transplant, the use of immunosuppression increases the risk of gastrointestinal cancer further and also the prevalence of other types of cancer (e.g. skin).
    - CF transplant recipients younger than 50 years have a 5-year absolute risk of 0.3% for colorectal cancer whereas CF patients older than 50 years have a risk of 6.4%.
    - **According to the CF Foundation, in transplanted CF patients, screening for colonic cancer with colonoscopy is recommended within two years of the transplant from the age of 30 (except when there has been a negative colonoscopy within the past 5 years). Continued rescreening is recommended every 5 years, unless a shorter interval is indicated by the findings of the most recent colonoscopy.**
    - The prevalence of post-transplant lymphoproliferative disease (PTLD) in CF is about 8.6%. Epstein-Barr virus (EBV) negative recipients who undergo EBV seroconversion (EBV positive donor or primary EBV infection after transplant) are at a higher risk.

4.13 Psychological and psychiatric manifestations

- Anxiety and depression are common in CF, however underreported, and their prevalence increases with age.
    - Anxiety has been reported in up to 31% of adult CF patients.
    - Prevalence of depression ranges around 29-46% and correlates with pulmonary function and the frequency of pulmonary exacerbations.
    - Prevalence of anxiety and depression from national and international patient registries is often based on self-reports and might be underestimated.
- Anxiety and depression are associated with poor health outcomes (decreased treatment adherence, missed appointments, risky behaviors such as smoking, alcohol or drug abuse, worse QoL, higher healthcare utilization and health care costs).
- Screening for anxiety and depression is recommended during patient follow-up to allow early intervention.

4.14 Advanced care planning (ACP)

- With CF adults growing older, discussions about the evolution of the disease and end-of-life issues become more important.

- Surveys revealed that even though the majority of adults with CF thought about and communicated with family about advance care wishes, only a minority reported such discussions with the physician.
- Although, timing varies significantly among CF centers, advanced care planning often occurs late in the course of the disease. With the better understanding of the complexity of CF, current practice is improving.

4.15 Main goals of CF care

- The mainstay of CF care consists of
  - early diagnosis
  - early initiation of treatments augmenting mucociliary clearance and mucous drainage
  - optimal nutritional support
  - early initiation of antimicrobial and anti-inflammatory therapies (if indicated)
  - early treatment of respiratory exacerbations
  - aggressive eradication of first *Pseudomonas aeruginosa* airway isolation
  - early identification and treatment of pulmonary and extra-pulmonary complications
  - effective infection control and segregation
  - continuous care at specialized CF centers with a multidisciplinary team
- Treatment at a specialized CF center ensures frequent visits and periodic routine tests leading to preventive strategies and early intervention when complications are identified. This plays a crucial role in improving outcomes in CF.
- Treatments targeting to correct or modify the CFTR defect are evolving rapidly. Ideally, they should be offered to patients at specialized CF centers. Personalized medicine is expected to play a major role in the management of CF patients in the next years.

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