A formalized transition program in cystic fibrosis: a ten-year retrospective experience of 97 patients in Lyon.

Gaelle Bourgeois[1], Fanny Magne[1], Stephane DURUPT[2], Raphaele NOVE-JOSSERAND[2], Philippe Reix[3], Isabelle Durieu[4], and Quitterie Reynaud[1]

[1]Centre Hospitalier Lyon-Sud
[2]Hospices Civils de Lyon, Centre Hospitalier Lyon Sud
[3]hôpital debrousse
[4]Hospices Civils de Lyon. UCBL1

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Abstract

Introduction: The prognosis of cystic fibrosis (CF) has dramatically changed over the past decade in France, mostly due to global improvements in specific care. Currently, the majority of French CF patients are adults, meaning they went through a transition process from a pediatric CF center to an adult CF center. To determine the impact of that transfer on clinical evolution, we report the transition procedure of our CF center in Lyon. Materials and Methods: From January 2006 to December 2016, 117 CF patients went through a standardized transition process from the pediatric to the adult CF center of Lyon. We compared the clinical evolution of the patients over 3 periods starting the year before transfer and ending the next year after transfer. Clinical data taken into account were FEV1%, BMI, pulmonary colonization, number of antibiotic courses, and number of days of hospitalization per year and outpatient visits per year. Results: No significant differences were observed between respiratory and nutritional status, pulmonary colonization, number of antibiotic courses, and numbers of hospitalizations and visits when comparing the 3 periods of observation (the year before, the year after and the next year after transfer) around transition. Conclusion: The standardized procedure of transition in Lyon is associated with the maintenance of a stable clinical status of our CF patients.

Introduction

Cystic fibrosis (CF) is one of the most frequent severe genetic diseases, with 6757 patients included in the French CF Registry in 2017 (1). The prognosis of CF has improved greatly thanks to early diagnosis and specific treatments and the establishment of specific CF centers. These improvements have led to significant demographic changes. Since 2013 in France, more than half of the French CF population are adults, indicating that almost all the pediatric CF patients have gone through the process of transition from a pediatric to an adult CF center. This phenomenon will continue to grow in the years to come. Transition between the pediatric and adult healthcare system is defined as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health (2). This period is described as a risky period, with potential complications or clinical degradation, which can include unsteadiness in young diabetic patients, solid organ transplantation rejection in young transplanted patients, and loss of follow-up in young patients with congenital cardiomyopathies or cancer (3). According to the systematic review of Crowley and al., limitation of transition complications in adolescents with chronic conditions is linked to specific transition clinics and the patient's education.

Currently, in France, there is no recommended national transition program for CF patients (4). Worldwide, practices for CF patient transfer are disparate. In Canada, a transition process has existed in some hospitals since 1982 (5), Australia and the US have been developing transition procedures for many years, and Australia has dedicated adult clinics for CF with positive results (6, 7). Focusing on Europe, the United Kingdom was a pioneer in the transition for patients with CF, with well-defined NHS protocols for years (8,9). Conversely, Germany and Denmark have no official transition programs for CF, but some studies on short-term program transitions have shown encouraging results within the past few years (11, 12).

Studies on transfer in CF mainly focus on subjective criteria and psychological criteria. Our study aimed to evaluate a ten-year-old, formalized transition process from a pediatric to an adult CF center in Lyon and observed its impact on the patients' clinical evolution.

Materials and methods

All patients with CF with a first visit at the adult CF center of Lyon from January 2006 to December 2016 were included if they were previously followed in the pediatric CF center of Lyon. There were no exclusion criteria. The follow-up lasted 3 years, starting one year before transfer until two years after. In both pediatric and adult CF centers, follow-up and medical care were similar: spirometry (with VC, FEV) testing and microbiological sputum analysis (sputum were analyzed in the same bacteriology laboratory using the same microbiological technique of analysis) every 3 months, inhaled therapy, inhaled or systemic antibiotics, respiratory physiotherapy, diabetes care, food and vitamin supplementation, and pancreatic enzyme supplementation. Patients visit their CF center every 3 months for a medical examination.

The first visit to the adult CF center was defined as the "transition day" and was named Y0. Its date was defined by pediatricians and occurred for patients between 17 and 20 years old after obtaining their agreement in a period of clinical stability. Teams from both centers (including physicians and paramedics) met for the transition day at the adult CF center. The same electronic medical files were shared by the two centers. The transfer process was the same for every patient.

Y-1 was defined as the visit one year before transition day at the pediatric CF center. Y+1 and Y+2 were the visits one and two years after transition day, respectively, in the adult CF center. Data were collected retrospectively from medical files annually throughout the study period (Y-1, Y0, Y+1, Y+2). The clinical data extracted were age at transfer, sex, CFTR genotype, respiratory function status (FEV1 liter), and BMI (kg/m^2). Microbiological data concerning chronic pulmonary colonization were extracted:*Pseudomonas aeruginosa* , *Staphylococcus aureus* ,*Stenotrophomonas maltophilia* , *Burkholderia cepacia* , nontuberculous mycobacteria and *Aspergillus* spp. Multidrug-resistant *Pseudomonas aeruginosa* (MRPA) was defined as a strain of *Pseudomonas* resistant to at least 3 classes of main anti-*Pseudomonas* antibiotics, such as monobactam/cephalosporins/penicillins, carbapenems, fluoroquinolones or aminoglycosides. Numbers of intravenous and oral antibiotics courses, days of hospitalization, and visits at the CF center were also recorded during the follow-up.

Statistical considerations

Quantitative data collected at Y-1, Y0, Y+1 and Y+2 were summarized using mean and standard deviation and were compared using Student's t-test. Descriptive data were expressed in percent and compared using Fisher's Test. Figures 1 to 3 show the distributions of the variables separately for groups A (0), A (1) and A (2). In order to compare these distributions, we use Wilcoxon's signed rank test. This test is used for paired data, the null hypothesis being that the distributions of the two samples are identical. The p-values of the tests comparing A (0) and A (1) respectively, and A (1) and A (2) are indicated in green. The only test rejected at the 10% threshold is for the number of consultations between A (0) and A (1) ($p = 0.059$). Figures 4 and 5 show the distribution of the differences between the groups (from left to right) A (0) and A (-1), A (1) - A (0) and A (2) - A (1) for the different variables. We use the same Wilcoxon test as before to compare them. This time the two tests are rejected at the 10% threshold for VEMS but neither is rejected for BMI. Analyses were executed with Python 2.7, scipy 1.1.0.

Results

Patient characteristics

Ninety-seven patients were included, consisting of 46 males (47.4%) and 51 females (52.6%). A total of 56% of the patients were delF508 homozygous. The mean age at transfer was 18.8±0.6. None of the patients underwent transplantation or died during the study period.

Pulmonary function evolution

The mean changes in FEV1 were -7.0±22.6% for the first period [Y-1-Y0], -2.1±16.8% for the second [Y0-Y+1] and +0.9±12.1% for the last period [Y+1-Y+2]. The difference between FEV1 change between the first and the last period was significatively significant, with an improvement for [Y+1-Y+2] (p value <0.01).

No significant difference was observed between the periods [Y-1-Y0] and [Y0-Y+1] for FEV1. There was a trend to a significant difference between [Y0-Y+1] and [Y+1-Y+2], p=0.056, with higher FEV1 in the period [Y+1-Y+2]. Data are summarized in Figure 1.

Nutritional status evolution

Concerning BMI, mean changes were, respectively, -1.0 ±5.2%, -0.1±6.0% and -0.7±6.5% for [Y-1-Y0], [Y0-Y+1] and [Y+1-Y+2].

There was no significant difference concerning mean BMI evolution over the 3 periods compared. The results are summarized in Figure 2.

Pulmonary colonization evolution

We observed no significant change in pulmonary colonization during the 3 periods around transition for *Staphylococcus aureus (SA),*including *MSSA* and *MRSA* , *Pseudomonas aeruginosa (PA),* including *MSPA* and *MRPA, Stenotrophomonas maltophilia (SM), Burkholderia cepacia (BC),* nontuberculous mycobacteria (NTM), and *Aspergillus fumigatus* . Data are summarized in Table 1.

Antibiotic courses evolution

We recorded averages of 1.1±1.4 intravenous antibiotic courses for [Y-1-Y0], 1.2±1.3 for [Y0-Y+1] and 1.1±1.2 for [Y+1-Y+2].

No difference between the number of antibiotic courses was observed between the 3 periods concerned. Data are summarized in Figure 3. For oral antibiotic courses, patients had an average 1.6±1.3 of courses per year for the first period, 1.3±1.4/year for the second period and 1.1±1.1/year for the last period. We compared the number of oral antibiotic courses per year before and after transfer ([Y-1-Y0] versus [Y+1-Y+2]), and we found that after transfer, patients had significantly fewer oral antibiotic courses per year.

Days of hospitalization and outpatients' visits evolution

The number of days of hospitalization per year was not significantly different for the 3 periods compared: we registered 0.3±0.7 days/year during [Y-1-Y0], 0.4±0.9days/year during [Y0-Y+1] and 0.4±0.8 days/year during [Y+1-Y+2], with a p value of p=0.21 between [Y-1-Y0] and [Y+1-Y+2]. Data are shown in Figure 4. The number of outpatient consultations per year for each patient was not significantly different between the 3 periods: there were 5.8±2.4 days/year, 5.2±2.1 days/year and 5.4±2.6 days/year for [Y-1-Y0], [Y0-Y+1] and [Y+1-Y+2], respectively. The results are shown in Figure 5. No patient was lost to follow-up.

Discussion:

According to our results, we observed no significant difference before and after transition for the main clinical prognosis criteria: pulmonary function, nutritional status, pulmonary colonization, hospitalizations and visits, and antibiotic courses.

The literature regarding transition in CF is focused on its perception by patients themselves and by members of the team and revealed that patients did not feel sufficiently empowered or prepared to transition (10–12). Previous articles tried to define a program for the transition process; it appeared to be difficult because each patient had different needs and did not feel ready at the same time (13). Patients' and caregivers' teams thought that transfer was more difficult when the preparation was not sufficient, particularly with patients' reluctance, lack of maturity or severe condition. According to the authors, a successful transition relies on a progressive process that includes patient empowerment.

In Lyon, such a procedure has been set up since 2006 (4) and currently seems to be effective, with stable clinical and microbiological settings all along the transfer process. No patient was lost to follow-up despite their youth. Our article focused on objective data that ensure that transition is successful.

A similar study was conducted in Paris and reported that transferring from a pediatric center to an adult center after a special preparation avoids a negative impact on respiratory function or on BMI evolution just after transition (14). It showed that a well-prepared transition from a pediatric center to an adult center for CF care was crucial. However, this study was published more than ten years ago, and transfer occurred in older patients.

Focusing on Europe, in Germany (15), adult CF patients are often followed in pediatric wards. In this country, short-term programs of transition are under process, with encouraging results in clinical and microbiological features, but they are not yet generalized. Welsner and al described a transition program for 39 German patients and showed that this process was linked to stability of respiratory function, BMI and microbiological data and to an increase of outpatient's consultation following transfer. In Denmark, Skov and al described transition in 40 patients, with no impact on respiratory function, BMI or quality of life (16).

A Belgian study showed that transition in cystic fibrosis is linked to worsening of FEV and FVC and increasing of *Pseudomonas aeruginosa*colonization, which highlights the fragility of patients during this period and enhances the importance of a transition program (17).

In North America, currently, some CF patients remain in pediatric centers for CF, but some encouraging data have shown the benefits of transfer on respiratory function (18). An American retrospective study demonstrated that patients transferring from a pediatric center to an adult center had a trend not to worsen their FEV versus patients remaining in pediatric centers (18). In both, the transfer process was followed by increasing numbers of outpatient consultations and of respiratory exams, perhaps because of anxiety in reaction to the transfer (14,18). In our study, outpatient consultations were not more frequent after transfer.

In Canada, a transition process has existed in a few hospitals for decades; its impact has been evaluated only on subjective data and showed improvement of quality of life for adults undergoing transition to an adult center (5).

Adolescence and early adulthood are difficult periods in a lifetime for people suffering from chronic diseases and are often linked to a worsening of health conditions (3). As such, patients with CF have to be managed in a formalized transition program to prevent such issues. One of the strengths of our study is that the totality of the 97 patients completed the entire follow-up period, and all participated in the same standardized transition program, with the use of common tools in both centers (informatics files and medical records) and well-defined protocols of care. Furthermore, our evaluation of transition included several objective criteria all along the transition process. Our study shows some limitations: it was a monocentric study, and we focused on objective parameters, without satisfaction evaluations of the transition process for the patients or caregivers.

Our ten-year experience of a formalized program for transition in CF allows for patients to maintain a stable medical situation over this risky period of transition.

Recently, major innovations for CF patient treatment were worked out, particularly CF triple therapy, with impressive results on FEV on 2019 (19,20), which may revolutionize the CF course.

It appears essential to associate these therapeutic innovations with strong transition programs between pediatric and adult centers for CF.

Abbreviations:

ABPA: Allergic bronchopulmonary aspergillosis

AF: *Aspergillus fumigatus*

BC: *Burkholderia cepacia*

BMI: Body mass index

CF: Cystic fibrosis

CFTR: Cystic fibrosis transmembrane conductance regulator

CRCM: Centre de Ressources et de Compétences pour la Mucoviscidose

FEV: Forced expiratory volume

MRPA: Multidrug-resistant *Pseudomonas aeruginosa*

MRSA: Methicillin-resistant *Staphylococcus aureus*

MSPA: Multisensitive *Pseudomonas aeruginosa*

MSSA: Methicillin-susceptible *Staphylococcus aureus*

SM: *Stenotrophomonas maltophilia*

NTM: Nontuberculosis Mycobacterium

PA: *Pseudomonas aeruginosa*

References

1. registre_francais_de_la_mucoviscidose_-_bilan_des_donnees_2016.pdf [Internet]. [cité 23 janv 2019]. Disponible sur: https://www.vaincrelamuco.org/sites/default/files/registre_francais_de_la_mucoviscidose_-_bilan_des_donnees_2016.pdf

2. Rosen DS, Blum RW, Britto M, Sawyer SM, Siegel DM, Society for Adolescent Medicine. Transition to adult health care for adolescents and young adults with chronic conditions: position paper of the Society for Adolescent Medicine. J Adolesc Health Off Publ Soc Adolesc Med. oct 2003;33(4):309-11.

3. Crowley R, Wolfe I, Lock K, McKee M. Improving the transition between paediatric and adult healthcare: a systematic review. Arch Dis Child. juin 2011;96(6):548-53.

4. Durieu I, Reynaud Q, Nove-Josserand R. [Transition from paediatric to adult cystic fibrosis care centre]. Rev Pneumol Clin. fevr 2016;72(1):72-6.

5. Gravelle AM, Paone M, Davidson AGF, Chilvers MA. Evaluation of a Multidimensional Cystic Fibrosis Transition Program: A Quality Improvement Initiative. J Pediatr Nurs. janv 2015;30(1):236-43.

6. ACFDR-2017-Annual-Report_highres_singles.pdf.

7. Sawicki GS, Ostrenga J, Petren K, Fink AK, D'Agostino E, Strassle C, et al. Risk Factors for Gaps in Care during Transfer from Pediatric to Adult Cystic Fibrosis Programs in the United States. Ann Am Thorac Soc. 2018;15(2):234-40.

8. Nazareth D, Walshaw M. Coming of age in cystic fibrosis – transition from paediatric to adult care. Clin Med. oct 2013;13(5):482-6.

9. Connett GJ, Nagra A. Ready, Steady, Go – Achieving successful transition in cystic fibrosis. Paediatr Respir Rev. 1 juin 2018;27:13-5.

10. Flume PA, Anderson DL, Hardy KK, Gray S. Transition programs in cystic fibrosis centers: perceptions of pediatric and adult program directors. Pediatr Pulmonol. juin 2001;31(6):443-50.

11. Anderson DL, Flume PA, Hardy KK, Gray S. Transition programs in cystic fibrosis centers: perceptions of patients. Pediatr Pulmonol. mai 2002;33(5):327-31.

12. Flume PA, Taylor LA, Anderson DL, Gray S, Turner D. Transition programs in cystic fibrosis centers: perceptions of team members. Pediatr Pulmonol. janv 2004;37(1):4-7.

13. Malbrunot-Wagner A-C, Bonnemains C, Troussier F, Darviot E, Chiffoleau M, Person C, et al. Passage de l'enfant a l'adulte : l'exemple d'un centre de ressources et de competences pour la mucoviscidose. Arch Pediatrie. 1 mars 2009;16(3):235-42.

14. Dugueperoux I, Tamalet A, Sermet-Gaudelus I, Bourgeois ML, Gerardin M, Desmazes-Dufeu N, et al. Clinical Changes of Patients with Cystic Fibrosis during Transition from Pediatric to Adult Care. J Adolesc Health. 1 nov 2008;43(5):459-65.

15. Welsner M, Sutharsan S, Taube C, Olivier M, Mellies U, Stehling F. Changes in Clinical Markers During A Short-Term Transfer Program of Adult Cystic Fibrosis Patients from Pediatric to Adult Care. Open Respir Med J. 30 juin 2019;13:11-8.

16. Skov M, Teilmann G, Damgaard IN, Nielsen KG, Hertz PG, Holgersen MG, et al. Initiating transitional care for adolescents with cystic fibrosis at the age of 12 is both feasible and promising. Acta Paediatr. 2018;107(11):1977-82.

17. Louage A, Knoop C, Hanssens L. [Impact of the transition period from childhood to adulthood in cystic fibrosis]. Rev Mal Respir. 16 janv 2020;

18. Tuchman L, Schwartz M. Health Outcomes Associated With Transition From Pediatric to Adult Cystic Fibrosis Care. Pediatrics. 1 nov 2013;132(5):847-53.

19. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial - The Lancet [Internet]. [cite 29 mai 2020]. Disponible sur: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32597-8/fulltext

20. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med. 7 nov 2019;381(19):1809-19.

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