Prognosis and treatment of 46 Chinese pediatric cystic fibrosis patients

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Abstract

Background: Since public awareness of cystic fibrosis (CF) has increased, more children have been diagnosed with CF in China. This study aimed to investigate medical and other challenges faced by pediatric CF patients in China.

Method: Treatments and treatment outcomes were retrospectively analyzed for 46 pediatric CF patients diagnosed from August 2009 to June 2019.

Results: Of 46 pediatric CF study patients, four died (one of pulmonary infection, one of severe respiratory failure, two of unknown causes) and five were lost to follow-up. Thirty-seven patients were monitored for 0.03 to 9.21 years; patients exhibited fewer attacks of respiratory tract infections after diagnosis (4.49 ± 2.13 episodes/year before diagnosis VS 1.97 ± 1.87 times/year after 1-year treatment, $p < 0.05$), significantly reduced sputum production and experienced 1.62 ± 1.71 exacerbations/year. Patient mean body mass index was 16.87 ± 3.53 and pancreatic malfunction persisted in 15 patients. Of the 28 children older than 6 years of age, 17 received lung function tests during follow-up; no significant differences were observed between lung function at follow-up and at diagnosis (FEV_1: 82.45% ± 16.56% vs 75.26% ± 22.34%, FVC: 87.18% ± 13.64% vs 86.99% ± 19.95%, $FEF_{75\%}$: 46.51% ± 28.78% vs 36.63% ± 24.30%, P = 0.27, 0.97, 0.20, respectively). In 27 cases with sputum results at follow-up, *Pseudomonas aeruginosa* was detected in 17 (62.97%), persisted in 14, newly emerged in 3 and was eliminated in 5 cases. Computed tomography lung scans of 22 cases revealed increased bronchiectasis in 6 cases after 2-60 months of treatment, decreased bronchiectasis in 3 cases after 2-96 months of treatment and unchanged bronchiectasis in 13 cases treated for 5-60 months. Twenty-four patients complied with aerosolized therapy, azithromycin, pancreatic enzymes and nutritional intake-based treatments, while 9 patients once stopped aerosolized therapy or azithromycin and 4 patients stopped all medications. Overall, azithromycin and tobramycin treatments were administered for 0.5-62 months and 0.5-48 months, respectively, and triggered no obvious adverse reactions.

Conclusion: No obvious deterioration of clinical presentation or lung function were found in Chinese pediatric CF patients after receiving standard therapeutic and active treatments, although malnutrition and low compliance were persistent challenges.

Introduction

Cystic fibrosis (CF) is a common life-limiting autosomal recessive genetic disorder, with highest prevalence in Europe, North America and Australia. The disease is caused by mutations within the *CFTR* gene that encodes a chloride-conducting transmembrane channel, the cystic fibrosis transmembrane conductance regulator (CFTR), which regulates anion transport and mucociliary clearance within airways [1]. CF can cause abnormalities in respiratory, digestive, endocrine and reproductive systems, with patient prognosis depending largely on the extent of lung involvement. Early nutritional intervention and monitoring to detect respiratory and gastrointestinal disease in infants with CF is vital for improving long-

term outcomes [2]. Since 1938, when cystic fibrosis was first identified, more and more cases have been reported worldwide [3].However, epidemiological reporting of incidence rates has been limited in China until recently. Indeed, only about 70 cases of Chinese children with CF have been reported, of whom most have been diagnosed only within the past few years. For these patients, treatment compliance, patient challenges and treatment outcomes remain unclear. Here, we retrospectively reviewed patient records in order to better understand challenges faced by children with cystic fibrosis in China.

Subjects And Methods

Patients

Forty-six children diagnosed with CF at the Second Department of Respiratory Medicine of Beijing Children's Hospital affiliated with Capital Medical University from August 2009 to June 2019 were included. A diagnosis of cystic fibrosis was mainly based on clinical manifestations, family history, positive sweat test and/or gene mutations of *CFTR* [4]. Informed Consent was obtained from parents and/or legal guardians of the participants. The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Beijing Children's Hospital, Capital Medical University, National Center for Children's Health with the number [2021]-E-034-R.

Methods

Clinical data were retrospectively analyzed and assessed. Variables of age, gender, onset age, age at diagnosis, presence of mutation, clinical manifestations, body mass index, lung function, bacterial colonies, complications, treatments and patient outcomes were recorded.

Statistical analysis

Quantitative data were presented as the Mean ± SD for continuous values; numbers (%) for categorical values and non-parametric data were presented as median and extreme values.

Results

1. Characteristics of patients

Patient characteristics at initial assessment are shown in Table 1. Patient mean age of onset was 4.05 ± 3.77 years (ranging from 0 to 12 years old) and mean age at diagnosis was 8.05 ± 4.26 years (ranging from 0.59 to 15.88 years). Fifty-one *CFTR* mutations were detected, with c.2909G > A and c.1000C > T detected most frequently (5 cases) and one child found to be homozygous for c.1521-1523delCTT (F508del). Respiratory symptoms included persistent coughing (46/46), wheezing (12/46) and hemoptysis (4/12). Other main manifestations included pancreatic insufficiency, sinusitis and malnutrition. Thirty-eight children completed sweat conductive tests and had values ranging from 45 to 168 mmol/l (108.55 ± 25.68 mmol/l). Thirty-one children over 6 years of age completed lung functional

assessments, with 19 cases showing different degrees of obstruction (mild to severe). Meanwhile, most patients (33/46) harbored *Pseudomonas aeruginosa* (*Pa*) infections that were detected at first admission, with 5 cases effectively clearing *Pa* and 14 failing to clear *Pa* during treatment.

Table 1
Clinical features of 46 Chinese CF patients at the time of diagnosis

Variables	N = 46
Sex –no (%)	46
Female - no (%)	20 (43.48%)
Male - no (%)	26 (56.52%)
Onset age -year	4.05 ± 3.77 (0–12, median2.50)
Age at diagnosis -year	8.05 ± 4.26 (0.59–15.88, median 8.74)
Duration of disease -year	4.01 ± 3.72 (0.14–12.44, median 3.05)
Pulmonary symptoms	
Cough -no/total no (%)	46/46 (100.00)
Wheezing -no/total no (%)	12/46 (26.09)
Extra pulmonary symptoms	3/46 (6.52)
1.	4.49 ± 2.13
Pancreatic malfunction –no/total no (%)	18/46 (39.13)
ABPA -no/total no (%)	14/46 (30.43)
Asthma -no/total no (%)	10/46 (21.74)

Plus–minus values are means ± SD

ABPA: Allergic bronchopulmonary aspergillosis, PA: Pseudomonas aeruginosa, SA: Staphylococcus aureus. Mild obstruction: FEV1 ranges from 60–80%, Moderate obstruction: FEV1 ranges from 40–60%, Severe obstruction: FEV1 less than 40%.

Variables	N = 46
Mutations in more than 2 children n (%)	5/46 (10.87)
c.2909G > A-no/total no (%)	5/46 (10.87)
c.1000C > T-no/total no (%)	3/46 (6.52)
c.263T > G -no/total no (%)	2/46 (4.35)
c.532G > A -no/total no (%)	2/46 (4.35)
c.2834C > T-no/total no (%)	2/46 (4.35)
c.595C > T -no/total no (%)	2/46 (4.35)
c.262-266delTTATA -no/total no (%)	2/46 (4.35)
c.2036G > A-no/total no (%)	2/46 (4.35)
c.1766 + 5G > T-no/total no (%)	2/46 (4.35)
c.293A > G -no/total no (%)	2/46 (4.35)
c.1409T > A-no/total no (%)	2/46 (4.35)
c.374T > C -no/total no (%)	2/46 (4.35)
c.3196C > A -no/total no (%)	
Lung function -no/total no (%)	31/46 (67.39)
FEV1	75.44% ± 22.40%
FVC	83.59% ± 16.99%
FEF75	39.45% ± 26.68%
Bacterial colonies n (%) -no/total no (%)	46/46 (100.00)
PA -no/total no (%)	33/46 (71.74)
SA -no/total no (%)	9/46 (19.57)
CT scan	46/46 (100.00)
Bronchiectasis -no/total no (%)	42/46 (91.30)
Inflammation -no/total no (%)	4/46 (8.70)
Plus–minus values are means ± SD	
ABPA: Allergic bronchopulmonary aspergillosis, PA: Pseudomonas aeruginosa, SA: Staphylococcus aureus. Mild obstruction: FEV1 ranges from 60–80%, Moderate obstruction: FEV1 ranges from 40–60%, Severe obstruction: FEV1 less than 40%.	

2. Treatment measures

The major aim of long-term treatment, airway clearance, was pursued using daily inhalation therapy of hypertonic saline and intermittent treatments with tobramycin, with nutritional support and azithromycin treatment provided as needed.

Azithromycin was prescribed in 34 cases and was administered orally for three days per week at a dosage of 10 mg/kg per day (as recommended for long-term use). Three children were not prescribed azithromycin due to their mild CF symptoms; at follow-up, two of them lacked *Pa* infection and *Pa* had been eradicated in the third. Of 34 children prescribed azithromycin, only 31 received this antibiotic regularly for 0.5 to 62 months (25.69 ± 16.78 months). Azithromycin discontinuation occurred in 3 children with mutations c.2909G > A, c.223C > T, c.1367delT and c.1657C > T because they had no symptoms or exacerbations. No obvious side effects of treatment were observed, except for one case with elevated liver enzymes and 2 cases with abdominal pain that was relieved after short-term azithromycin cessation.

With regard to tobramycin, the injected tobramycin was used here in place of the nebulized form, since the nebulized form is not available in China. For children over 6 years of age, a 300-mg dose was administered twice daily; for younger children, we instead used a dose of 160mg. Tobramycin treatment alternated between 28-day administration and 28-day cessation. Ultimately, 29 children received tobramycin treatment to eradicate or prevent *Pa* infection over a 0.5- to 48-month time period (24.60 ± 13.40 months). Overall, 5 cases effectively cleared *Pa* infection after treatment with intravenous antibiotics. However, 14 cases still harbored *Pa* after receiving treatment, while 3 other patients with prior tobramycin treatment histories for *Pa* infection prevention were infected with *Pa* afterwards.

With regard to airway management, the lack of professional physiotherapists in China has led to assignment of CF treatment management responsibilities to respiratory doctors, nurses and parents. Moreover, nutritional guidance has just begun to be provided in China and multi-disciplinary outpatient guidance is still extremely limited. Nevertheless, our follow-up evaluations revealed that 20 children could tolerate daily postural drainage, manual chest percussion and vibration-based measures provided by our current system of caregivers.

3. Treatment adherence

Most of our pediatric CF patients resided in rural areas, have attained a low level of education and belonged to families shouldering heavy economic burdens. Their parents struggled to administer long-term treatments (fraught with side effects) to their children. Thus, poor adherence to recommended airway clearance measures, poor nutrition and irregular medication administration frequently occurred. Nevertheless, 24 of our cases strictly complied with doctors' prescriptions and regular follow-up visits. Meanwhile, 9 other patients once stopped aerosolized therapy or azithromycin, 3 others stopped taking all medicines for one year and 1 patient stopped for two years, all without aggravating their symptoms.

4. Clinical outcomes

Forty-six children were monitored for more than 0.03 to 9.21 years (2.88 ± 1.72 years). Generally, patients maintained irregular hospital visits, with intervals of 0.5 to 12 months between visits or between exacerbations. Of the 46 total cases, 4 children died (3 girls and 1 boy) and 5 cases were lost to follow-up.

4.1 Fatal cases

One patient who died of a pulmonary infection had provided a sputum sample at the time of the first hospital visit that produced positive *Pa* culture results, while another patient died of respiratory failure attributed to a diagnosed infection with *Pa* and Aspergillosis. The parents of the other two fatal cases were reluctant to reveal causes of death. These patients were seriously ill at time of diagnosis; all presented with diffuse bronchiectasis, while two cases had digestive system involvement and two cases had histories of irregular treatment compliance.

4.2 Patient survival

All 37 surviving children presented with the symptom of mild cough that was most evident in autumn and winter and during early morning and/or night. During treatment, attacks of respiratory tract infections were reduced from 4.49 ± 2.13 to 1.97 ± 1.87 ($P < 0.05$), as were severities of coughing and sputum production. However, during treatment these patients still experienced 1.62 ± 1.71 episodes of exacerbation that required oral, inhaled or intravenous antibiotics over the study follow-up period, although the severities of attacks in most children were lower than in non-survivors. Notably, 3 cases remained basically stable without additional treatment. Of the 28 children over 6 years old, 17 (60.71%) who completed lung function tests during follow-up, findings for 9 children were normal, while lung obstructions of 5 were mild, of one was moderate and of 2 were severe. Failures of patients to complete pulmonary function testing may reflect conditional restrictions imposed by local hospitals that bar testing of young children. Nevertheless, after comparing follow-up test results with results at diagnosis, no significant differences were observed in lung function (FEV_1: 82.45% ± 16.56% vs 75.26% ± 22.34%, FVC: 87.18% ± 13.64% vs 86.99% ± 19.95%, $FEF_{75\%}$: 46.51% ± 28.78% vs 36.63% ± 24.30%, $P = 0.27, 0.97, 0.20$ respectively). Meanwhile, of 27 (72.97%) patients who provided sputum samples, microbiological testing revealed that 17 were infected with *Pa* and 6 harbored *Staphylococcus aureus* in airways during acute attacks. Post-treatment, *Pa* infection persisted in 14 cases, with new emergence detected in 3 cases and elimination of *Pa* in 5 cases. Patient mean body mass index was 16.87 ± 3.54 (ranging from 12.74 to 26.12), while pancreatic malfunction persisted in 15 children that did not improve with treatment. At treatment completion, all 37 surviving children were able to tolerate mild physical exertion and 33 of them could even attend school. Ultimately, lung CT scans of 22 survivors revealed increased bronchiectasis in 6 cases after treatment for 2 months to 5 years, decreased bronchiectasis in 3 cases after treatment for 2 months to 8 years and no change in bronchiectasis in 13 cases after treatment for 5 months to 5 years. Assessment of the 37 children after long term treatment at follow up are shown in Table 2.

Table 2
Follow up assessment of the 37 children after long term treatment

Variables	**N = 37**
Follow up duration -year	2.88 ± 1.72 (0.03–9.21, median 2.83)
Pancreatic malfunction -no/total no (%)	15/37 (40.54)
BMI	16.87 ± 3.54
BMI Z-score	-0.78 ± 1.46
Acute exacerbation times	1.62 ± 1.71
Respiratory infection times after treatment	1.97 ± 1.87
Lung function -no/total no (%)	17/37 (45.95)
FEV1	75.26% ± 22.34%
FVC	86.99% ± 19.95%
FEF75	36.63% ± 24.30%
Change of lung function –no/total no (%)	17/37 (45.95)
Better -no/total no (%)	7/17 (41.18)
Worse -no/total no (%)	10/17 (58.82)
Bacterial colonies -no/total no (%)	27/37 (72.97)
PA -no/total no (%)	17/27 (62.96)
SA -no/total no (%)	6/27 (22.22)
Changes of bronchiectasis -no/total no (%)	22/37 (59.46)
Decrease -no/total no (%)	3/22 (13.64)
Unchanged -no/total no (%)	13/22 (59.09)
Increase -no/total no (%)	6/22 (27.27)
Plus–minus values are means ± SD	

Discussion

Our study analyzed treatment outcomes for a cohort of 46 Chinese children with CF who were monitored for three years on average. Generally, clinical phenotypes and the genotypic spectrum associated with Chinese pediatric CF cases differ from corresponding aspects of Caucasian cases [5]. To date, 51 genomically distinct mutations have been identified in Chinese cases, with c.2909G > A and c.1000C > T ranking highest in frequency (10.87%). Due to the greater diversity of genotypes and phenotypes

observed in Chinese CF cases as compared to Caucasian cases, treatment responses and prognoses are likely more variable for Chinese CF patients than for Caucasians, but testing of this presumption awaits results of large-scale studies focused on Chinese CF patients.

Pulmonary function testing is used to assess the severity of CF lung disease, with FEV_1 testing especially useful for this purpose [6]. Although 17 children in this study received regular follow-up care to maintain lung function, no overall significant difference was observed between pulmonary function at diagnosis versus that at follow-up. However, improved pulmonary function observed in some patients may be explained by timely treatment, shorter follow-up times or milder disease, emphasizing the fact that such testing should be used more frequently to monitor pulmonary function of the youngest CF patients. With regard to pulmonary infection monitoring, of 27 patients who completed sputum culture examinations at diagnosis, 5 cases received additional sputum culture examinations at follow-up that showed they had effectively cleared *Pa* during the follow-up period. Moreover, 13.64% of children exhibited improvement of bronchiectasis symptoms that was attributed to effective treatment delivery that aligned with results of follow-up testing that revealed that *Pa* infections trended downward, although *S. aureus* detections trended upward. Nevertheless, routine pulmonary infection testing of pharyngeal swabs or collected sputa should be conducted by outpatient clinics in China in order to improve treatment delivery and clinical status.

Antibiotics are indispensable for achieving control of chronic pulmonary infections and acute exacerbations in CF patients. However, use of long-term oral antibiotics, including azithromycin and tobramycin, to control infection is not recommended, as shown in a study by Samson et al. Their results demonstrated that the beneficial effect of low-dose tobramycin treatment disappeared with prolonged administration beyond 12 months and thus did not outweigh potential risks associated antibiotic use [7]. Meanwhile, another clinical trial-based study was stopped in spite of a clinical benefit (increased time to first pulmonary exacerbation in the azithromycin-treated group), due to a lack of impact on patient microbiological outcomes that increased antimicrobial resistance risk [8]. In this study, overall azithromycin treatment of roughly 2-years duration after initiation at 3 months after diagnosis (on average) did not trigger obvious adverse reactions or drug resistance. Thus, we speculate that longer-duration treatments may be feasible if they are accompanied by intensive monitoring for side effects and antibiotic drug resistance.

Treatment of pediatric CF patients with inhaled tobramycin after first *Pa* detection has become standard practice during the past decade at most CF centers, since tobramycin use was not associated with detectable renal toxicity or ototoxicity in preschoolers with CF [9]. Here, intravenous tobramycin treatment during acute exacerbations seemed to have a beneficial effect on bacterial clearance rate and expectorate quantity in our study, but further studies are needed to evaluate safety of intravenous tobramycin treatment in pediatric CF patients.

Importantly, lack of nutritional intake has been a major weakness of CF management efforts in China. Because CF patients rarely receive guidance from nutritionists, parents must often adjust patient diets

themselves. As is well known, BMIs of pediatric CF patients and adolescents aged 2–18 years should be greater than 50% of BMIs of healthy children of the same sex within the same age range [10]. However, only 11 children (29.72%) in this study received adequate nutrition, as recommended by accepted guidelines. Nevertheless, calculations based on CF patient data entered into the CF Foundation Annual Data Report 2014 indicated that the proportion of children aged 2–19 years old with acceptable BMIs was 55% [11]. Moreover, 10 children (27.03%) had BMIs lower than the fifth percentile of the same age group. These results reveal that malnutrition is a common and serious concern for pediatric CF patients in China that may be tied to the lack of specialized nutritionists in China, lack of awareness by respiratory physicians of this issue and poor patient living conditions. Factors that aggravate patient malnutrition include repeated chronic infections, discontinuation of drugs, poor compliance, pancreatic exocrine dysfunction and poor basic nutritional status. Most notably, the number of patients with pancreatic malfunction of the total number of CF patients was 18 of 46 (39.13%) at baseline and 15 of 37 (40.54%) at follow-up. Although the incidence rate of pancreatic malfunction was not very high, we advocate for inclusion of appropriate pancreatic enzyme replacement therapy within long-term treatment plans for these patients.

Another problem we faced was a low follow-up rate. Generally, treatment adherence of patients with chronic diseases rarely exceeds 80%, with adherence most often falling between 30% and 70% [12]. CF is a relentless disease that, even with complete adherence, leads to declining health of survivors that continues even into adulthood [13]. CF guidelines recommend that patients receive at least 4 clinical visits per year, lung function testing every 6 months and yearly culture-based microbiological testing of respiratory tract secretions. Each visit should include a routine physical examination, pulmonary tests and collection of sputum or cough swab cultures for microbiological assessment as part of a multi-disciplinary approach to care. In a 2017 study, more than half of patients with CF complied with recommendations relating to clinical visits, respiratory culture-based testing and lung function testing [14]. However, in other studies only 40% of patients met care guidelines, as reported by the Department of Pediatrics, St. Louis University School of Medicine in 2009 and 2010[15], although this percentage was greater than the 2002 rate of 24.6%. Similarly, although 24 patients in this study completely followed doctors' prescriptions and engaged in regular follow-up visits, patient compliance was still insufficient. Thus, improved doctor-delivered patient education, regular follow-up reminders, specialized outpatient treatment and access to CF regional centers may be needed to improve patient compliance in China. Indeed, one study in France demonstrated that implementation of a tracking system significantly improved patient quarterly clinic visit attendance from 4.6 ± 2.3 in 2009 to 6.3 ± 4.6 in 2013 ($P < 0.0001$) as one solution for patient non-compliance[15].However, other challenges causing patient noncompliance may be related to long travel distances to health providers and insufficient recognition or understanding of CF disease that in China are of greater significance than in western countries. Moreover, financial issues, work and school conflicts and difficulties associated with clinical scheduling may be addition obstacles to patient compliance.

During follow-up we learned that 4 fatalities had occurred that may have stemmed from severe illness, insufficient treatment adherence by some parents and unavailability of pediatric lung transplantation in

China for patients with chronic respiratory failure. Notably, 3 survivors remained stable without receiving long-term medication or daily airway cleaning that they might not have needed due to their mild disease severity. Conversely, CT findings in another 3 cases indicated worsening lung pathology at follow-up, although airway cleaning every day had led to reduced amounts of expectorated sputum and numbers of acute respiratory tract infections.

Our research had limitations. First, data were obtained from a single center and thus might not adequately represent all Chinese children with CF. Moreover, follow-up measures were not of sufficient quality or duration, while missing data prevented analysis of some variables. Nevertheless, our results highlight the need for improved CF patient quality of care and case management and should be confirmed in future investigations of larger patient cohorts to better understand challenges facing the Chinese CF population.

In conclusion, diverse CF severity, low patient compliance and insufficient long-term management by medical providers are challenges that CF patients currently face. Although we did not observe obvious deterioration of clinical status and lung function in our patients, malnutrition and low patient compliance should have received greater focus in this study. Nonetheless, our results highlight the need for better systematic follow-up to improve pediatric CF patient management. We thus recommend that greater efforts be made to deliver standardized and individual care management, strengthen education measures and provide comprehensive follow-up care beginning early in childhood to pediatric CF patients in China.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of *Beijing Children's Hospital, Capital Medical University, National Center for Children's Health* with the number [2021]-E-034-R. Informed Consent was obtained from parents and/or legal guardians of the participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current report are available from the corresponding author (Shunying Zhao) on request

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Authors' contributions

Concept and Design: SZ, Data Collection or Processing: QC and YS, Clinical cases analysis: HX, XT, HY, Interpretation and Drafting of the manuscript: QC, Revised the manuscript: SZ. All authors read and approved the final manuscript.

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Supplementary Files

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- Clinicaldataof46ChineseCFpatients.xlsx
- supplementaltable.docx