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Clinical, Immunological, and Microbiological Aspects of Cystic Fibrosis in Children: Optimization of Management Tactics

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ABSTRACT: Cystic fibrosis (CF) remains one of the most significant hereditary diseases, characterized by a severe progressive course, multisystemic involvement, and high medico-social significance. This study aimed to comprehensively analyze the clinical, immunological, and microbiological aspects of CF in children to develop and substantiate differentiated therapeutic approaches. A total of 28,449 medical histories were retrospectively analyzed, identifying 307 children with CF (1.04%). A prospective study included 106 children with a mixed form of CF (aged 1 month to 14 years), 35 children with recurrent bronchitis with broncho-obstructive syndrome (RB+BOS), and 20 healthy controls. The study employed clinical, functional (spirometry), immunological (cellular and humoral immunity, cytokine profile), microbiological (sputum and stool cultures), and biochemical (vitamin D) methods. The investigation revealed a high prevalence of nutritional deficiency (88.2%), predominant combined ventilatory disorders (62.5%), and significant immunological imbalance characterized by T-lymphocyte depletion, elevated pro-inflammatory cytokines (IL-8, TNF- α), and vitamin D deficiency (86.8%). Microbiological analysis showed a predominance of *P. aeruginosa* (45.3%) and *S. aureus* (30.2%) in the respiratory tract, with a high frequency of intestinal dysbiosis (86.8%). Differentiated therapy, including an immunomodulator (IRS-19), a probiotic (*Saccharomyces boulardii*), and nutritional support, demonstrated the highest efficacy in Group III, leading to a 29.0% increase in FEV1, normalization of nutritional status, a 2.3-fold reduction in exacerbation frequency, and eradication of *P. aeruginosa* in 64.0% of patients. The developed management algorithm, based on a validated risk stratification scale (sensitivity 82%, specificity 76%), allows for personalized therapy and significantly improves the prognosis and quality of life for children with CF.

INTRODUCTION

Cystic fibrosis (CF), or mucoviscidosis, is a severe autosomal recessive hereditary disease caused by mutations in the CFTR gene (Cystic Fibrosis Transmembrane Conductance Regulator). This condition leads to a dysfunction of the exocrine glands, resulting in the production of excessively viscous secretions that affect primarily the respiratory and digestive systems, as well as other organs. Despite significant advances in diagnosis and therapy, CF remains a major challenge for healthcare systems worldwide. According to the World Health Organization (WHO), CF affects approximately 1 in 2,500–3,500 newborns in Europe and North America, with significant variations depending on the population. The first symptoms typically appear in 65% of children before six months of age, in 80% before one year, and in 90% before two years [1; 4c, 2; 84c].

The problem of timely diagnosis and proper management of patients with CF is relevant globally. The evolution of diagnostic methods, from clinical observation to genetic and functional testing, reflects significant progress in understanding the genetic basis and pathophysiology of the disease [3]. The discovery of the CFTR gene in 1989 was a pivotal moment, paving the way for understanding the etiopathogenetic mechanisms and clinical diversity of CF [4]. To

date, over 2,000 variants of the CFTR gene have been described, with 360 clinically significant mutations listed on the CFTR2 website. These mutations are classified into seven main classes based on their impact on protein function, which is crucial for selecting targeted therapy [5, 6].

In the Republic of Uzbekistan, the problem of CF has not been sufficiently studied for a long time. There were no national registries, and mass neonatal screening was only introduced in 2025. Previous research by Fayzullaeva N.Ya. et al. (2018) focused on identifying significant allelic associations of the CFTR gene in children with CF and their mothers, developing a coefficient of shift in immunological parameters and a prognosis index [7]. However, a thorough analysis of the frequency of CF in children, the role of vitamin D, and the microbiome of the respiratory tract has not been conducted. This gap in knowledge, combined with the need for effective treatments in the context of limited access to CFTR modulators, underscores the relevance of this study.

The role of the microbiome in CF pathogenesis is a rapidly evolving field. The concept of the "gut-lung axis" highlights the systemic influence of gut microbiota on pulmonary immunity. Children with CF exhibit profound dysbiotic changes in both the respiratory and intestinal tracts, with chronic colonization by *P. aeruginosa* being a key factor in disease progression [8, 9]. The gut microbiome of infants with CF matures slower and is less diverse than that of healthy children, which can impact overall health and immune development [10].

The therapeutic landscape for CF has been revolutionized by CFTR modulators, which aim to restore the structure and function of the defective protein [11, 12]. However, their high cost and limited availability in many countries, including Uzbekistan, make the optimization of basic and symptomatic therapy critically important. The search for effective, affordable, and pathogenetically justified treatment regimens, including immunomodulation, probiotic correction, and nutritional support, remains a priority.

This study aims to conduct a comprehensive, multicomponent analysis of the clinical, immunological, and microbiological aspects of cystic fibrosis in children to develop and scientifically substantiate a differentiated approach to therapy and prevention of severe disease progression.

MATERIALS AND METHODS

The study was conducted at the Republican Specialized Scientific and Practical Medical Center of Pediatrics (RSSPMCP) of the Ministry of Health of the Republic of Uzbekistan and the Regional Children's Multidisciplinary Medical Center (RCMMC) of Namangan region from 2022 to 2024.

The work was carried out in two stages. At Stage I, a retrospective analysis of 28,449 medical histories of children hospitalized with bronchopulmonary pathology was performed. Among them, 307 children with a confirmed diagnosis of CF were identified, which constituted 1.04%. The gender distribution was 139 girls (45.2%) and 168 boys (54.7%). The majority of children (74.6%) were aged 1-10 years.

At Stage II, a prospective, in-depth clinical, laboratory, functional, immunological, and microbiological study was conducted on a cohort of 106 children with a mixed form of CF, aged from 1 month to 14 years. The comparison group consisted of 35 children with recurrent bronchitis with broncho-obstructive syndrome (RB+BOS). The control group included 20 practically healthy children of the same age.

The diagnosis of CF was verified based on comprehensive clinical and instrumental studies, including a sweat test (using the "Nanoduct" and "Macroduct" systems) and molecular genetic testing for CFTR gene mutations in borderline cases.

RESEARCH METHODS:

Clinical and Anamnestic: Assessment of complaints, medical history, physical examination, and nutritional status evaluation using Z-scores for weight and height.

Functional: Computer spirometry was performed on a BTL-08 Spiro Pro spirometer (UK) for children over 5 years old. Parameters analyzed included FEV1, FVC, FEV1/FVC (Tiffeneau index), MEF25, MEF50, MEF75.

Immunological: Assessment of cellular immunity (CD3+, CD4+, CD8+, CD16+, CD20+ lymphocytes, phagocytic activity of neutrophils - PAN) using antilymphocyte antibodies (Research Institute of Immunology, Moscow). Humoral immunity was assessed by measuring serum levels of IgA, IgM, IgG, and circulating immune complexes (CIC). Cytokine profile (IL-

1 β , IL-4, IL-8, TNF- α , IFN- γ) was determined by ELISA using a "Multiskan FC" analyzer (Finland). Serum 25-hydroxyvitamin D (25(OH)D) levels were measured by ELISA (IDS, UK).

Microbiological: Bacteriological examination of sputum and deep oropharyngeal swabs was performed quarterly. Stool samples were cultured on selective and differential-diagnostic media to assess intestinal microbiome composition. Antibiotic sensitivity was determined by the disk-diffusion method. ESBL production was detected using the double-disk method.

Statistical: Data were processed using Microsoft Office Excel-2016 and Statistica 10.0. Parametric and non-parametric methods were used, calculating mean (M), standard error (m), and relative values (%). Significance was assessed using Student's t-test and Fisher's exact test. Correlation analysis was performed using Pearson's method (r).

RESULTS AND DISCUSSION

Clinical and Functional Characteristics

The retrospective analysis revealed a 2.4-fold increase in newly diagnosed CF cases from 2024 (n=23, 6.9%) to 2025 (n=54, 16.4%), likely due to improved diagnostics. The age at diagnosis varied widely, with only 9.7% of children diagnosed within the first year of life, indicating late diagnosis before the introduction of neonatal screening.

The clinical picture of the 106 prospectively studied children was characterized by a universal involvement of the respiratory and digestive systems (100% chronic obstructive bronchitis and pancreatic insufficiency). Nutritional deficiency was highly prevalent: 88.2% of children had a body mass deficit, with 43.5% showing severe protein-energy malnutrition (Z-score -2 to -3). The most common symptoms are presented in Table 1.

Table 1. Main Clinical Symptoms in the Examined Children (n=106)

Symptom	CF Children (n=106)	RB+BOS Group (n=35)	p
Respiratory			
Wet cough	78.3%	94.3%	<0.05
Difficulty in nasal breathing	19.8%	51.4%	<0.001
Dyspnea (mixed)	50.9%	91.4%	<0.001
Gastrointestinal			
Fatty stool (steatorrhea)	92.4%	0%	<0.001
Frequent, bulky, foul-smelling stool	66.9%	2.8%	<0.001
Abdominal bloating/pain	77.3%	5.7%	<0.001
Hepatomegaly	78.3%	11.4%	<0.001

Symptom	CF Children (n=106)	RB+BOS Group (n=35)	p
Physical Signs			
"Drumstick" fingers	56.6%	0%	<0.001
Dullness of lung sound	32.1%	0%	<0.001
Moist rales	83.0%	22.8%	<0.001
Crepitation	74.5%	11.4%	<0.001

Spirometry revealed that in children with CF, the combined type of ventilatory impairment was predominant (62.5%), indicating both obstructive and restrictive changes. The mean FEV1 was $42.03 \pm 0.9\%$, FVC was $49.52 \pm 1.05\%$, and the Tiffeneau index was $56.18 \pm 1.03\%$, which were significantly lower than in the comparison group ($p < 0.001$). A pronounced decrease in MEF75 ($32.05 \pm 1.60\%$) indicated early involvement of small airways.

Immunological Profile and Cytokine Status

The study revealed a pronounced immunological imbalance in children with CF. A significant decrease in the relative content of CD3+ ($38.09 \pm 1.12\%$ vs $65.2 \pm 6.4\%$ in control, $p < 0.001$), CD4+ ($20.81 \pm 0.54\%$ vs $39.1 \pm 2.1\%$, $p < 0.001$) lymphocytes was noted, along with a decrease in phagocytic activity ($31.18 \pm 1.02\%$ vs $58.5 \pm 2.3\%$, $p < 0.001$). The immunoregulatory index (CD4+/CD8+) was significantly reduced to 1.08 ± 0.06 compared to 2.0 ± 0.1 in the control group ($p < 0.001$). The humoral response was characterized by hyperimmunoglobulinemia: a 1.6-fold increase in IgA (131.33 ± 5.16 mg% vs 107.9 ± 3.6 mg%, $p < 0.01$) and a 1.4-fold increase in IgG (1412.63 ± 4.73 mg% vs 938.3 ± 17.6 mg%, $p < 0.001$).

The cytokine profile showed a pronounced pro-inflammatory shift. As shown in Table 2, there was a significant increase in IL-1 β , IL-8, and TNF- α , and a decrease in IFN- γ .

Table 2. Comparative Analysis of Cytokines in Children with CF and RB+BOS ($M \pm m$)

Parameter	Healthy (n=20)	RB+BOS (n=35)	CF Children (n=106)	p (CF vs Control)
IL-1 β , pg/ml	27.80 ± 2.60	85.05 ± 7.80	138.62 ± 8.20	<0.001
IL-4, pg/ml	4.60 ± 0.60	18.60 ± 1.20	24.60 ± 1.50	<0.001
IL-8, pg/ml	19.20 ± 2.40	59.27 ± 2.41	89.54 ± 2.45	<0.001
TNF- α , pg/ml	28.40 ± 1.50	45.20 ± 2.50	71.20 ± 3.60	<0.001
IFN- γ , pg/ml	34.30 ± 2.70	20.60 ± 1.80	15.80 ± 1.00	<0.001

Correlation analysis revealed a strong direct correlation between IL-8 levels and the frequency of exacerbations ($r=+0.72$; $p<0.001$), and a strong inverse correlation between TNF- α and FEV1 ($r=-0.68$; $p<0.001$).

Vitamin D Status

A high prevalence of vitamin D deficiency was found in children with CF. The average level of 25(OH)D was 16.8 ± 1.9 ng/ml, which was 2.2 times lower than in the control group (36.2 ± 0.4 ng/ml; $p<0.001$). Deficiency (<20 ng/ml) was registered in 47.2% of children, and insufficiency (20-30 ng/ml) in 39.6%. Only 13.2% had a normal level. Inverse correlations were found between 25(OH)D and the frequency of exacerbations ($r=-0.58$; $p<0.001$), as well as with the levels of pro-inflammatory cytokines IL-1 β ($r=-0.51$), IL-8 ($r=-0.54$), and TNF- α ($r=-0.49$).

Microbiological Landscape

The study of the respiratory tract microbiota showed a predominance of *P. aeruginosa* (45.3% including mixed infections) and *S. aureus* (30.2%). The frequency of *P. aeruginosa* isolation increased with age, from 13.6% in children aged 0-2 years to 59.1% in those aged 7-18 years ($p<0.01$). A high level of antibiotic resistance was noted, with 69.2% of *Klebsiella* spp. and 46.2% of *E. coli* strains being ESBL producers. Intestinal dysbiosis was diagnosed in 86.8% of children with CF, significantly higher than in the comparison group (74.3%) and control group (20.0%) ($p<0.001$). A quantitative analysis revealed a profound deficit of obligate microbiota (a 20-30-fold decrease in *Bifidobacterium* and *Lactobacillus* spp.) and a significant overgrowth of opportunistic pathogens like hemolytic *E. coli*, *Klebsiella* spp., *S. aureus*, and *Candida* spp.

Efficacy of Differentiated Therapy

Based on the identified pathogenetic features, three therapeutic groups were formed for a 12-month prospective study:

Group I (n=21): Basic therapy.

Group II (n=23): Basic therapy + immunomodulator IRS-19 + probiotic Bioferol.

Group III (n=19): Basic therapy + IRS-19 + Bioferol + nutritional support (Infatrini).

The most pronounced positive dynamics were observed in Group III. A significant improvement in respiratory function was noted, with FEV1 increasing by 29.0% (from 42.0% to 54.2%; $p<0.01$) and FVC by 18.4% ($p<0.01$). The dynamics of FEV1 are presented in Figure 1.

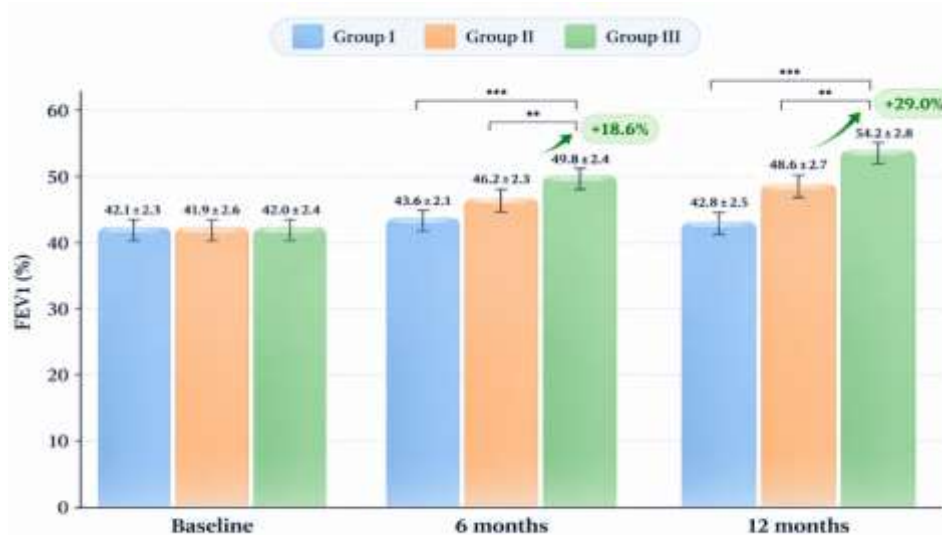


Figure 1. Dynamics of FEV1 in the study groups over 12 months.

The comprehensive therapy in Group III led to a normalization of nutritional status (Z-score improved from -2.2 to -0.8; $p<0.001$), a 2.3-fold reduction in the frequency of exacerbations (from 4.9 to 2.1 per year; $p<0.001$), and a 58.3% reduction

in hospitalizations. The eradication rate of *P. aeruginosa* was 64.0% in Group III, compared to 48.0% in Group II and 24.0% in Group I ($p < 0.01$).

The levels of pro-inflammatory cytokines significantly decreased in Group III: IL-8 decreased by 2.0 times ($p < 0.01$) and TNF- α by 1.9 times ($p < 0.001$). The vitamin D level increased from 16.8 ± 1.9 to 33.8 ± 3.8 ng/ml ($p < 0.001$), reaching the normal range. The quality of life, assessed by the PedsQL questionnaire, improved from 54.6 ± 4.2 to 76.4 ± 5.0 points ($p < 0.001$).

The high efficacy of the combined therapy can be explained by the synergistic effect of its components. IRS-19 provides systemic and local immunomodulation, enhancing phagocytosis and antibody production. Bioferol restores gut microbiome balance, reducing endotoxin load and systemic inflammation. Nutritional support with Infatrini provides the necessary substrates for anabolic processes and immune function restoration.

CONCLUSION

The comprehensive study of clinical, immunological, and microbiological aspects of cystic fibrosis in children has revealed a high prevalence of nutritional deficiency, severe immunological imbalance with a pro-inflammatory cytokine shift, profound dysbiosis of the gut and respiratory tract, and a high frequency of vitamin D deficiency. The identified correlations between these factors and the severity of the disease confirm their pathogenetic role.

The developed differentiated therapeutic approach, which includes an immunomodulator, a probiotic, and nutritional support in addition to basic therapy, has demonstrated high clinical efficacy. This strategy leads to a significant improvement in respiratory function, normalization of nutritional and immunological status, correction of dysbiosis, a reduction in exacerbation frequency, and an improvement in the quality of life of patients.

The validated risk stratification scale allows for the identification of children with a high risk of severe disease progression, enabling personalized and timely therapeutic intervention. The implementation of the developed management algorithm in pediatric practice can significantly improve the prognosis and quality of life for children with cystic fibrosis in the Republic of Uzbekistan.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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