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Forewords
Remesh Kumar R
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CHAPTER 10

Cystic Fibrosis: An Emerging Illness in India

Nitin Dhochak, Sushil Kumar Kabra

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive multisystem disorder characterized by chronic airway disease and fat malabsorption. It is the most common recessive life-limiting genetic condition in Caucasian population. Most western countries perform routine newborn screening for CF which leads to early diagnosis and optimization of care. Though initially considered to be a disease of western world, more and more children are diagnosed with CF in India since description of earliest cases in 1968.[1] Difference in mutation profile, delayed diagnosis, advanced disease in childhood, frequent malnutrition, and poor affordability to long-term medical care, pose special challenges in management of children with CF in India.[2] In this document, we will discuss the status of CF in India, innovations in diagnostic testing and treatment with special focus on developing world.

BURDEN OF DISEASE

Incidence of CF in Canada, United States, Western Europe, and Eastern Europe are approximately 1 in 3,300, 4,000, 4,500, and 6,000 live births respectively. More than 30,000 individuals live with CF in United States alone, while numbers are more than 70,000 worldwide.[3]

Due to gross underdiagnosis and lack of registries, true incidence of CF in India is unknown. Based on epidemiological studies among migrant population of Indian origin in USA and UK, incidence of CF in India was estimated to be 1 in 40,000 and 10,000 live births respectively.[4,5] In a study of cord blood samples from 995 newborns, F508del mutation was detected in 4 samples. Considering frequency of F508del homozygous cases ranging from 19 to 44%, overall incidence of CF was estimated between 1 in 43,321 and 100,323 live births.[6]

PATHOPHYSIOLOGY

Cystic fibrosis results from abnormalities in CF transmembrane conductance regulator (CFTR) protein transcribed by *CFTR* gene on long arm of

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chromosome 7 at position 7q13. CFTR is a cyclic AMP-regulated chloride channel present on apical membrane of airway epithelial cells. CFTR is functionally linked to calcium-dependent chloride channel and epithelial sodium channels (ENaC). In healthy state, extracellular shift of chloride ion maintains hydration of airway epithelial layer surface liquid. Decrease in CFTR function and overactive ENaC lead to dehydration of airway surface liquid. This leads to desiccated and acidic airway secretions and impaired ciliary dysfunction. Poor clearance of thick secretions leads to blockage of small airways leading to hyperinflation. Recurrent infections especially due to *Staphylococcus* and *Pseudomonas*, concentrated inflammatory mediators, and impairment of innate defenses gradually lead to recurrent pneumonia and bronchiectasis.[7] Thick viscid secretions in pancreas lead to blockage of pancreatic ducts, activation of enzymes, and pancreatic injury, eventually progressing to exocrine pancreatic insufficiency initially, followed by endocrine insufficiency. Poor resorption of chloride ions in sweat leads to excessive losses of electrolytes in sweat which can result in hyponatremia, hypochloremia and dehydration in hot weather; renin-angiotensin system activation further leads to hypokalemia and metabolic alkalosis, also known as pseudo-Bartter syndrome.[8]

GENETICS

More than 2,000 mutations causing CF have been identified, affecting CFTR expression at different steps. Traditionally *CFTR* mutations are described in five classes, newer classification systems have proposed up to seven classes.[9] Classification of mutations is summarized in **Table 10.1**.

Cystic fibrosis being an autosomal recessive disorder requires *CFTR* gene mutation on both chromosomes for disease manifestations. The mutation can be same on both chromosomes (homozygous) or different (compound heterozygote). Class I, II, III and VII usually have severe defects and are associated with severe lung disease and pancreatic exocrine insufficiency. Class IV, V and VI have some residual CFTR activity, hence less severe lung disease and may have residual pancreatic exocrine function, but are predisposed for recurrent pancreatitis.[9]

Profile of CFTR Mutations

Worldwide, F508del is the most common mutation with varying frequency across regions. In UK, F508del constitute approximately 76% of all *CFTR* gene mutations; *G542X* and *G551D* are the other common mutations. Overall F508del constituted 65% of all *CFTR* mutation alleles in Europe; few countries had low frequency of the mutation (e.g., Turkey 27%, Tunisia 18%).[10] In USA, F508del constitutes nearly 65% of all *CFTR* mutations (44.2% homozygous and 40.5% heterozygous for F508del among all CF patients).[11]

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TABLE 10.1: *CFTR* mutation classification.

Class	*Defect*	*Examples*	*Potential therapies*
I	Immature stop codon, no protein synthesis	Gly542X, Trp1282X	Read through agents
II	Misfolded protein, retained and destroyed at endoplasmic reticulum	Phe508del, Asn1303Lys, Ala561Glu	Correctors + Potentiators
III	Impaired gating	Gly551Asp, Ser549Arg, Gly1349Asp	Potentiators
IV	Impaired conductance	Arg117His, Arg334Trp, Ala455Glu	Potentiators
V	Reduction in surface CFTR concentration, usually splice variants	Ala455Glu, 3272-26A→G, 3849+10 kb C→T	Antisense oligonucleotides, correctors, potentiators
VI	Unstable CFTR, increased endocytosis	c.120del23, rPhe508del	Stabilizers
VII	Large deletions, no mRNA production	dele2,3(21 kb), 1717-1G→A	Unrescuable

Source: De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med. 2016;4(8):662-74.

In Indian population, mutation profile is very different from western population as well as in different regions across India. Proportion of F508del among *CFTR* mutations varies between 19 and 44% in different studies.[12-16] Other common mutations included 1161delC, 3849+10kbC-T and S549N.[13,16] Children from Indian states of Jammu and Kashmir, Punjab, and Gujarat, had higher proportion of F508del mutation. Among children whose ancestors could be traced to Pakistan, 56% had F508del mutations compared to 12% in rest of the children.[12]

■ CLINICAL FEATURES

As most developed countries have newborn screening for CF, most of the patients are diagnosed in neonatal period and early infancy. These children are frequently asymptomatic at the time of diagnosis and early instillation of treatment delays the progression of pulmonary morbidity. Due to lack of newborn screening, relative rarity of disease, lack of awareness among pediatric physicians and lack of methods for diagnosis of CF, children are frequently diagnosed late when there is advanced pulmonary disease with bronchiectasis and *Pseudomonas* colonization along with malnutrition.[17] In studies performed between 2002 and 2003 in India, median age of diagnosis

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TABLE 10.2: Clinical manifestation of cystic fibrosis in India.

Clinical features	***n = 120***[12]	***n = 18***[19]
Symptoms		
Recurrent/persistent pneumonia	118 (98%)	13 (73%)
Chronic cough		14 (77.8%)
Recurrent wheezing		10 (55.6%)
Failure to thrive	108 (90%)	17 (94%)
Malabsorption	96 (80%)	9 (50%)
Recurrent sinusitis		5 (28%)
Dehydration	16 (13%)	
Rectal prolapse	16 (13%)	1 (5.6%)
Meconium ileus	10 (8%)	
Salty taste	5 (5%)	
Salt craving	5 (5%)	
Skin rashes	5 (5%)	
Vitamin D deficiency	4 (4%)	
Vitamin A deficiency	10 (8%)	
Pneumothorax/empyema	3 (3%)	
Meconium ileus equivalent	2 (2%)	
Deafness	2 (2%)	
Examination		
Severe malnutrition	50 (42%)	
Z-score for weight for age*	–2.59 (–3.01, –2.32)	
Clubbing	80 (75%)	13 (72%)
Chest hyperinflation	100 (83%)	
Crepitations	110 (92%)	
Rhonchi	40 (33%)	
Bronchial breathing	20 (17%)	
Nasal polyposis	5 (4%)	
CF score*	51 (20, 80)	

*Mean (95% confidence interval)
Source: References 12 and 19.

was 4.8 years and 30 months respectively.[12,18] More recently in 2019, though the median age of diagnosis has improved to 22 months, there is still gap of nearly 20 months between onset of symptoms and diagnosis (median age of onset of symptoms being 2.7 months).[2] Disease manifestations vary as per time of diagnosis in children. A summary of studies on clinical features in children with CF in India is presented in **Table 10.2**.

Clinical features also vary with age of the child. Age-specific manifestations of CF are summarized in **Table 10.3**.

Due to acidic secretion and thick dehydrated mucus, meconium is hardened and can cause obstruction at ileocecal junction antenatally or at birth. This is known as *meconium ileus.* Meconium ileus is seen in approximately 20% of neonates with CF. Neonates with meconium ileus have CF in 80–90% cases, necessitating evaluation for CF in all neonates with

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TABLE 10.3: Clinical features of cystic fibrosis according to age of child.

Age group	*Clinical features*
Neonatal period	• Meconium ileus, meconium peritonitis, bowel perforation • Prolonged neonatal jaundice • Persistent cough, hyperinflation, lung collapse
Infants	• Prolonged jaundice • Persistent cough, recurrent wheezing, recurrent pneumonia • Steatorrhea (may present once weaning feed is started) • Micronutrient deficiency (hemolytic anemia due to vitamin E deficiency, acrodermatitis enteropathica) • Hypoalbuminemia • Dehydration with electrolyte disturbances, especially in summer months (Hyponatremia, hypochloremia, hypokalemia, metabolic alkalosis; also known as Pseudo-Bartter syndrome) • Rectal prolapse
Toddlers and preschool children	• Recurrent and persistent pneumonia, chronic wet cough • Steatorrhea, malnutrition • Dehydration and electrolyte abnormalities • Micronutrient deficiency, especially fat-soluble vitamin deficiency • Distal intestinal obstruction syndrome (Meconium ileus equivalent) • CF-related liver disease • Rectal prolapse
School-going children	• Productive cough • Recurrent pneumonia • Bronchiectasis • ABPA • Steatorrhea • Distal intestinal obstruction syndrome (meconium ileus equivalent) • CF-related liver disease • Failure to thrive
Adolescents	• Chronic bronchiectasis and recurrent pneumonia • ABPA • CF-related diabetes • CF-related liver disease • Azoospermia • Depression and psychosocial abnormality • Hypertrophic pulmonary osteoarthropathy • Decreased bone mineral density

(ABPA: allergic bronchopulmonary aspergillosis; CF: cystic fibrosis)

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meconium ileus.[19] In childhood, similar presentation of intestinal obstruction is seen due to collection of hardened stools in ileocecal region, known as distal intestinal obstruction syndrome (DIOS).

At birth, airways are sterile in children with CF. Different organisms predominate in different age groups. *Haemophilus influenzae* and *Staphylococcus aureus* appear early in life (infants and children) while *Pseudomonas aeruginosa* infection occurs later (adolescents and adults) in developed countries.[20,21] Series from India suggest that *Pseudomonas* is frequently seen in infants and young children with CF.[22,23] In studies from India, *Pseudomonas* is the commonest agent isolated followed by *Burkholderia cepacia*, *Staphylococcus* species and *Acinetobacter*.[22] Other colonizing agents include fungi (*Aspergillus fumigatus*, *Candida* species, and *Mycobacterium tuberculosis*). Non-tubercular mycobacteria were not identified in any of the 104 children in an Indian study.[22]

Infants and toddlers may develop rectal prolapse; common contributing factors being constipation and straining, fat malabsorption, uncontrolled pulmonary disease and chronic cough, and malnutrition.[24] Rectal prolapse usually improves by correcting these factors.

During summer months, excessive water, and electrolyte loss due to excessive sweating with poor oral replenishment in infants and young children leads to dehydration with dyselectrolytemia (hyponatremia and hypochloremia). Renin-angiotensin axis-mediated water and sodium reabsorption and potassium excretion in kidney and sweat lead to hypokalemia. Metabolic alkalosis is due to contraction of extracellular fluid, hypochloremia, and secretion of hydrogen ion in kidneys.[25] In a few infants such episodes may be the presenting feature of CF.[8,25] These are frequently confused with Bartter syndrome.

As children grow older, bystander injury and progressive loss of beta cell in pancreatic islets lead to insulin deficiency. This is initially apparent in periods of high glucose loads (post-meal hyperglycemia with normal fasting blood glucose), which gradually progress to severe insulin insufficiency, known as CF-related diabetes (CFRD).[26] Other hypotheses point toward dysfunctional insulin and glucagon release by pancreatic islet cells due to primary dysfunction of CFTR channels. CFRD is present in 2% of children and 19% of adolescents. In adults, CFRD is seen in 40% of individuals in their 20s, and 45–50% of those aged ≥30 years.[27] In a study of Indian children with CF, 23% had abnormal glucose tolerance test (mean age 11 years).[28] Children with CFRD may present with typical diabetic manifestations of polyuria, polydipsia, weight loss or poor weight gain, and frequent pulmonary exacerbations.

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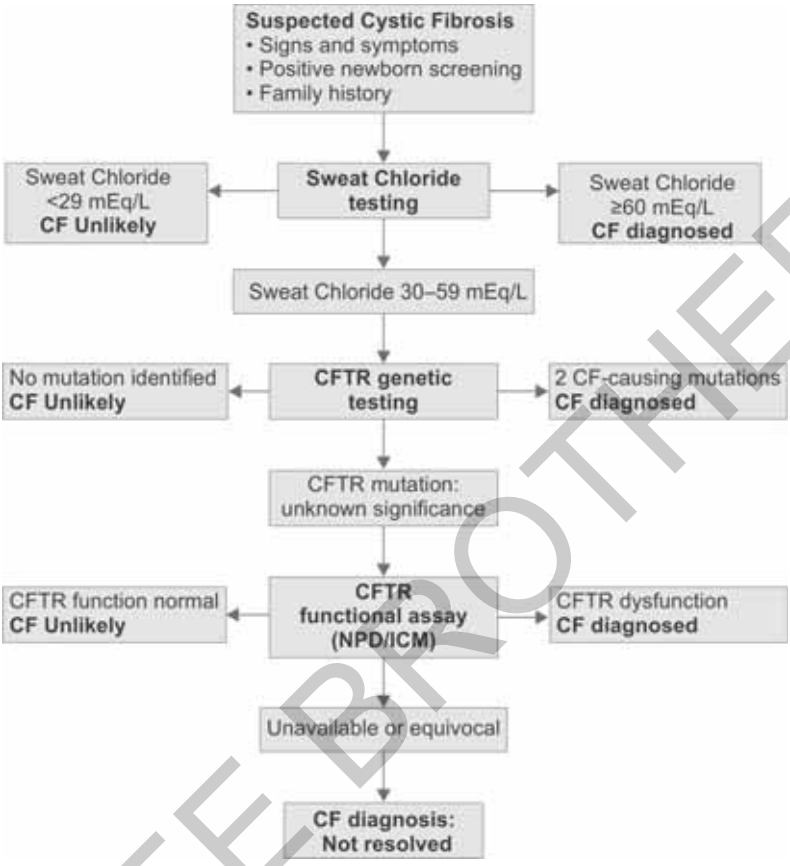
Flowchart 10.1: Diagnostic algorithm of cystic fibrosis.



DIAGNOSIS OF CYSTIC FIBROSIS

Diagnostic tests for CF include sweat chloride estimation, *CFTR* mutation analysis, and CFTR physiological testing [nasal potential difference (NPD) or intestinal current measurement (ICM)], preferably done sequentially in that order. Diagnostic algorithm based on Consensus Guidelines from the Cystic Fibrosis Foundation is described in **Flowchart 10.1**.[29]

Sweat Chloride Estimation

Sweat chloride estimation is first-line investigation in the diagnosis of CF. Elevated sweat chloride (≥ 60 mEq/L) is highly sensitive (99%) and specific (93%) for the diagnosis of CF.[30] The test includes two steps: (1) collection of sweat by pilocarpine iontophoresis, and (2) estimation of sweat chloride. Sweat chloride estimation should be performed in neonates > 36 weeks corrected for gestational age and > 2 kg weight, after 48 hours of life—preferably after 10 days of life, ideally by 28 days. Sweat chloride may be falsely elevated in the first 24 hours of life.[29]

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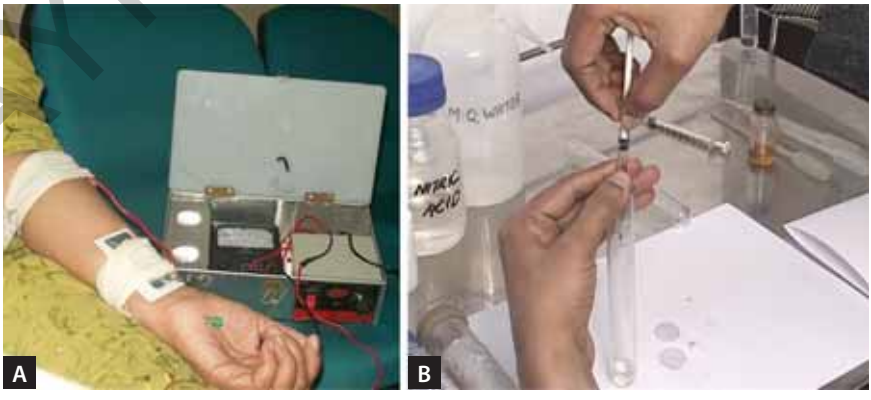
Sweat testing can be done using Gibson and Cooke method or Macroduct sweat test system. In Gibson and Cooke method, sweat production is stimulated by pilocarpine iontophoresis by passing current through a pilocarpine-soaked filter paper/gauze for 5 minutes. The stimulated area must be 2 inches by 2 inches (4 inches^2) and electrode must cover at least 2 inches.[2] Thereafter, a dry filter paper is applied to the stimulated area for up to 30 minutes for sweat collection. The minimum acceptable sweat weight is 75 mg. Sweat chloride estimation can be performed by chemical titration of chloride ions.[29] A commercially available Macroduct sweat testing system uses coil for collecting sweat (minimum required sweat amount is 15 μL) and automated chloridometer for estimation of chloride concentration.[30] Sweat chloride values of ≥ 60 mEq/L are considered as positive test, 30–59 mEq/L as intermediate and ≤ 29 mEq/L are considered as negative.

Availability of sweat chloride estimation system is scarce in India and is available only in limited centers. An indigenously made sweat collection system based on Gibson and Cooke method was devised which significantly reduced the cost of sweat chloride test **(Figs. 10.1A and B)**. Cost of this equipment was 7 US$ (500 rupees) and cost of each test was 0.5 US$ (35 rupees). The method had excellent repeatability (intraobserver variability of 2.5 ± 4.24 mEq/L, and interobserver variability of 1.12 ± 4.34 mEq/L).[31]

Causes of elevated sweat chloride other than CF may be untreated adrenal insufficiency, atopic dermatitis, hereditary nephrogenic diabetes insipidus, malnutrition, mucopolysaccharidosis, hypothyroidism, and glycogen storage disorder.

Mutation Analysis

Identification of two disease-causing mutations can be considered diagnostic of CF. Mutation analysis is useful in children with consistently borderline sweat chloride estimations. More than 2,000 mutations have been identified



Figs. 10.1A and B: (A) Indigenous sweat collection system; (B) Chloride titration by mercuric nitrate.

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in patients with CF. In Caucasian population, a small number of mutations identify large number of CFTR mutations. A panel of four most common mutations including F508del, G551D, G542X and 621+1G>T identify >80% of disease-causing CFTR mutations. Extended panels further increase the sensitivity.[32] Pathogenicity of CFTR mutations identified can be checked on online repository (https://www.cftr2.org/index.php). Due to very low frequency of F508del and wide variability in mutation profile in India, these mutation panels are not useful.[6]

Sequencing of *CFTR* gene can identify mutations in children where common mutations are not present and in areas where sweat testing is not available. But it is costly and frequently identifies mutations of unknown significance.

Apart from diagnosis, identification of CFTR mutations has significance in genetic counseling and antenatal screening of CF in future pregnancies, and eligibility for newer targeted therapies. It should be offered to all patients with diagnosed CF, especially when parents plan for further pregnancies.

CFTR Physiological Testing

Nasal potential difference (NPD) and intestinal current measurement (ICM) are tests to assess functional status of CFTR channels. In patients with intermediate sweat chloride and less than 2 disease-causing mutations, physiological testing can help in the diagnosis of CF.[33] Currently these tests are not available in India.

Basal NPD is more negative in children with CF. A larger change in potential is seen on blocking of Na channels by amiloride (representing hyperfunctioning of ENaC) in children with CF, and no change in potential is seen in response to CFTR stimulation by zero chloride solution and isoproterenol. Stimulation of other chloride channels by ATP shows normal response in both children with CF and healthy subjects. Limitations of NPD include lack of wide availability, and large variability in cut-offs (vary between labs) and intrasubject variability.

Intestinal current measurement is an ex vivo test, performed on rectal biopsy tissue sample. Response to stimulation by carbachol and histamine has two components: positive current by potassium efflux and negative current by chloride efflux through CFTR channel. In healthy subjects, chloride efflux masks potassium efflux, while in CF, current is reverse due to only potassium efflux.

Cystic Fibrosis Newborn Screening

In most developed countries, routine newborn screening is performed for CF. In most places, tiered screening approach is used. First tier test for CF screen is immunoreactive trypsinogen (IRT) by heal prick blood sample within

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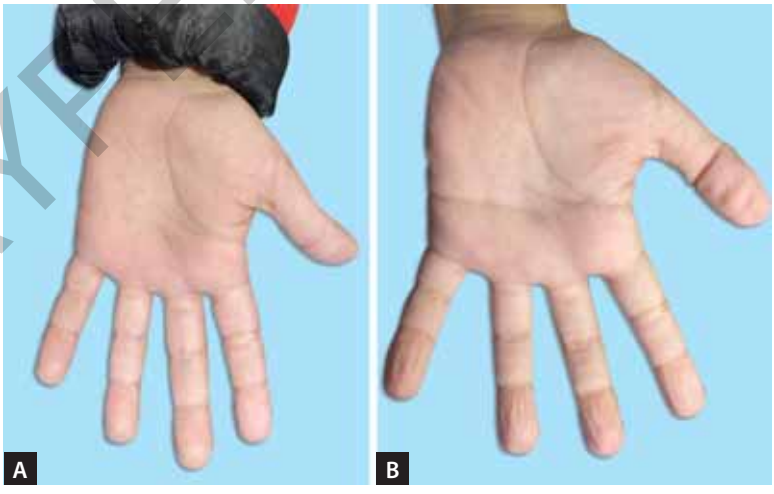
24–72 hours (marker of pancreatic injury). If IRT is elevated, child undergoes second tier screen, which varies in different places; could be repeat IRT (at 2–4 weeks), mutation panel or pancreatic-associated-protein. Patients with positive screen have to be confirmed for diagnosis by a confirmatory test (most commonly sweat chloride).[33]

In India, CF newborn screening is not a routine. As the sensitivity and specificity of IRT test is not very good, it cannot be used for making a diagnosis of CF. Confirmatory test is necessary for those positive on IRT screening. Patients with meconium ileus may have low IRT levels even with CF; so all children with meconium ileus should be evaluated by CF diagnostic tests. As CFTR mutations are highly variable in India, use of a panel of mutations is not a preferred second tier test.

If sweat test facility is not available, children with symptomatic disease and multiple suggestive features of CF including recurrent/persistent pneumonia with malabsorption, family history of CF, positive aquagenic wrinkling (see below), biochemical profile (metabolic alkalosis, hypochloremia, hyponatremia and hypokalemia) and *Pseudomonas* colonization in sputum, should receive treatment for CF pending confirmatory test as and when available.

Other Tests

Children with CF are predisposed to the development of early skin wrinkling on exposure to water. Aquagenic wrinkling of skin of palm and fingers on dipping of hand in room temperature water can be used as a screening diagnostic test in children with CF **(Figs. 10.2A and B)**. Using a cut-off of 3 minutes, aquagenic wrinkling has modest diagnostic accuracy for CF (sensitivity = 81% and specificity = 57%).[34]



Figs. 10.2A and B: Aquagenic wrinkling demonstrated in a child with cystic fibrosis. (A) Picture of hand before test; (B) Wrinkling seen after 3 minutes of immersion in water.

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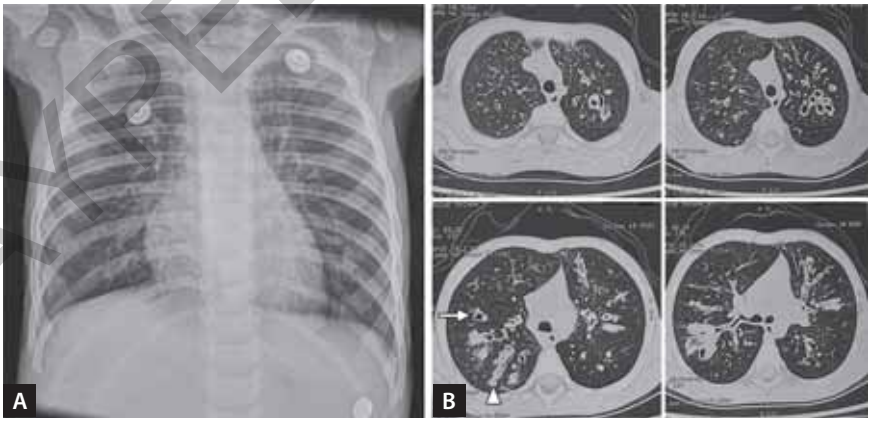
Other tests are aimed for the following:

- *Estimation of disease severity:* For example, pulmonary function tests and chest imaging.
- *Detection of complications of CF:* These include—(1) total IgE and aspergillus-specific IgE for allergic bronchopulmonary aspergillosis; (2) oral glucose tolerance test and HbA1c for CFRD; (3) liver function tests and ultrasound abdomen for CF-related liver disease; and (4) echocardiography for pulmonary arterial hypertension.
- *Tests for airway colonization*: Sputum or cough swab bacterial culture should be routinely done; sputum for fungus and non-tubercular mycobacteria in selected cases with high suspicion.
- *Tests for pancreatic function:* Fecal elastase, fecal fat estimation, and stool for fat globules.

Spirometry (FEV1) is traditionally used to monitor pulmonary function. Lung clearance index (LCI) based on multiple breath washout technique, which is calculated as cumulative expired volume at the point where end-tidal inert gas concentration falls below 1/40th of the original concentration, divided by the functional residual capacity (FRC). LCI has been shown to be a more sensitive test for identification of pulmonary involvement in CF, especially due to its ability to better evaluate lower airway disease.[35]

Imaging findings vary with age and disease severity. Infants may present with hyperinflation and peribronchial thickening, especially in upper zones **(Fig. 10.3A)**. Older patients may show typical bronchiectasis, mucous plugging, with or without pulmonary hypertension **(Fig. 10.3B)**.



Figs. 10.3A and B: (A) Chest X-ray of an infant with cystic fibrosis showing hyperinflation (flattened diaphragm) and increased bronchial markings; (B) Older child contrast-enhanced CT scan of chest showing diffuse bronchiectasis (arrow mark pointed to typical signet ring sign), and mucus plugging (arrowhead).

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MANAGEMENT

Management of children with CF can be divided into respiratory and non-respiratory therapies. Respiratory therapies include airway clearance therapy, management of pulmonary exacerbations and airway colonization, and complications such as ABPA, pulmonary hemorrhage. Nonrespiratory therapies include pancreatic enzyme replacement, fat-soluble vitamin and micronutrient supplementations, and management of complications such as DIOS/meconium ileus, CFRD, and CF-related liver injury.

Respiratory Management

Airway Clearance Therapy

The secretions in children with CF are thick, dry, and viscid. These are difficult to clear without specific efforts. Airway clearance therapies have two main objectives—(1) thinning of airway secretions, and (2) clearance of secretions from airways. The sequence followed is administration of a bronchodilator followed by inhaled mucolytic medications followed by chest physiotherapy to remove the thinned secretions. Adequate water and salt intake also helps in maintaining hydration of respiratory secretions.

Mucolytic agents: Commonly used mucolytic agents include recombinant human DNase, hypertonic saline (HS), inhaled mannitol, and N-acetyl cysteine (inhaled or oral).

Recombinant human DNase: Children with CF have high DNA content in respiratory secretions due to disintegration of neutrophils and inflammatory cells. Use of DNase is associated with improved lung clearance, decrease in pulmonary exacerbations, and decrease in lung function deterioration.[36] Dose of inhaled DNase is 2.5 mg (2.5 mL solution) by nebulization once daily (may be given twice daily in selected patients). Side effects include airway irritation, hypersensitivity, rash, chest pain, and conjunctivitis. It is not routinely available in India.

Hypertonic saline (HS): HS (3% saline and 7% saline) is used by nebulization to stimulate mucociliary clearance, increase hydration, and hence loosening of respiratory secretions. Though mechanism of DNase is different and there are no randomized control trials to compare HS and DNase, the relatively inexpensive HS can be used to enhance airway clearance. HS may cause bronchoconstriction and excessive coughing in some patients; hence salbutamol inhalation [by metered dose inhaler (MDI) or nebulization] is given before HS nebulization. Clinical trials between 3% and 7% HS showed slightly better lung function after 3% saline use.[37] HS nebulization should be given twice daily (usually 3–5 mL nebulization, may be given more frequently as needed) 15–30 minutes before chest physiotherapy session.

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- Advances in the various fields of pediatrics starting from neonatology and extending to development, nutrition, immunization, infectious diseases, adolescence, critical care, and different organ systems are presented with scientific evidence from recent publications.
- Newer insights in the fields of environment (noise pollution), child rights, genetics, and SARS-CoV-2 vaccines are some additional highlights of this volume.
- 27 chapters with at least one topic covered under each subspecialty.
- The chapters have been carefully prepared by eminent pediatricians across the country and abroad and peer-reviewed by equally illustrious colleagues.
- This compendium is aimed to update the knowledge of pediatricians across a wide spectrum, from pediatric residents to senior faculty, researchers, and consultants.

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Printed in India

Available at all medical bookstores or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road,
Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

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ISBN 978-93-5465-613-2