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Message from President

Dear Esteemed Colleagues,

Greetings from the Pediatrics Respiratory Society Delhi. We are ready yet again with another issue of our prestigious quarterly journal and the timing of its release makes it even more special. As we as a team prepare ourselves for the grand success of Delhi Respicon 2024- the flagship annual conference of our society, to be organized on 25th August 2024 at Dr. Passi Sabhagaar, Hindu Rao Hospital and North DMC Medical College, Delhi, we all will also witness the release of this special issue dedicated to various investigative modalities in the practice of Pediatric pulmonology.

The editorial board led by Dr. Anil Sachdev and Dr. Neetu Talwar has put exceptional hard work to make this issue a reality. They along with our extremely dedicated reviewers and talented contributors to the issue deserve a big applause and congratulations.

The Pediatrics Respiratory Society Delhi is committed to pursue and promote the agenda of excellence in pediatric pulmonology practice and is working swiftly towards the goal.

PRS office bearers and the organising team of Delhi Respicon 2024 thanks and congratulate all the members of PRS and delegates for being a part of this mega academic event.

Warm regards.

Dr. Rakesh K Dogra
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FORCED OSCILLATION TECHNIQUE (FOT): A COMPREHENSIVE REVIEW

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Abstract

The Forced Oscillation Technique (FOT) has recently emerged as a significant tool in respiratory medicine, offering a non-invasive, sensitive, and comprehensive assessment of lung function. This review aims to elucidate the principle of oscillometry, the various types of FOT and waveforms, the different machines available, the parameters measured and their interpretation, comparisons against spirometry, current and future applications, and the associated drawbacks.

Introduction

Lung function testing is crucial for diagnosing, monitoring, and managing respiratory diseases specially in asthma (1). Traditionally, spirometry has been the gold standard technique; however, it has limitations, particularly in-patient populations such as children, the elderly, and those with severe respiratory impairment (2). Patients who cannot perform forceful breathing manoeuvre as needed in spirometry, either due to poor neuromuscular reserves or post cardio-thoracic or abdominal surgery, also demand a reliable tool to monitor lung functions (2). Children with poor attention span or cognitive functions like autism and those suffering from various genetic-neurometabolic syndromes adds up substantially to the cohort of indigents. FOT, a much simpler and reliable alternative that measures respiratory mechanics by superimposing small pressure oscillations on the patient's normal breathing, is gaining attention in recent times. This technique provides detailed information about the mechanical properties of the respiratory system with minimal subjective efforts, offering potential advantages over traditional spirometry.

Principle of Oscillometry

Oscillometry is based on the principle that the respiratory system can be modelled as a combination of resistive, elastic, and inertive components. When pressure oscillations are applied to the respiratory system, the resulting flow response is measured. Oscillations produced by using a loudspeaker or an oscillating piston are forced on the respiratory flow generated during tidal breathing, hence named as Forced Oscillation Technique (FOT) (2). In-built pressure and flow transducers directly measure these parameters at individual frequencies after signal filtering. Later the relationship between the pressure and flow can be analysed to derive respiratory impedance (Zrs), which includes both resistance (Rrs) and reactance (Xrs), using ohm's law (Resistance = Pressure/Flow) by the machine (Figure 1) (2).

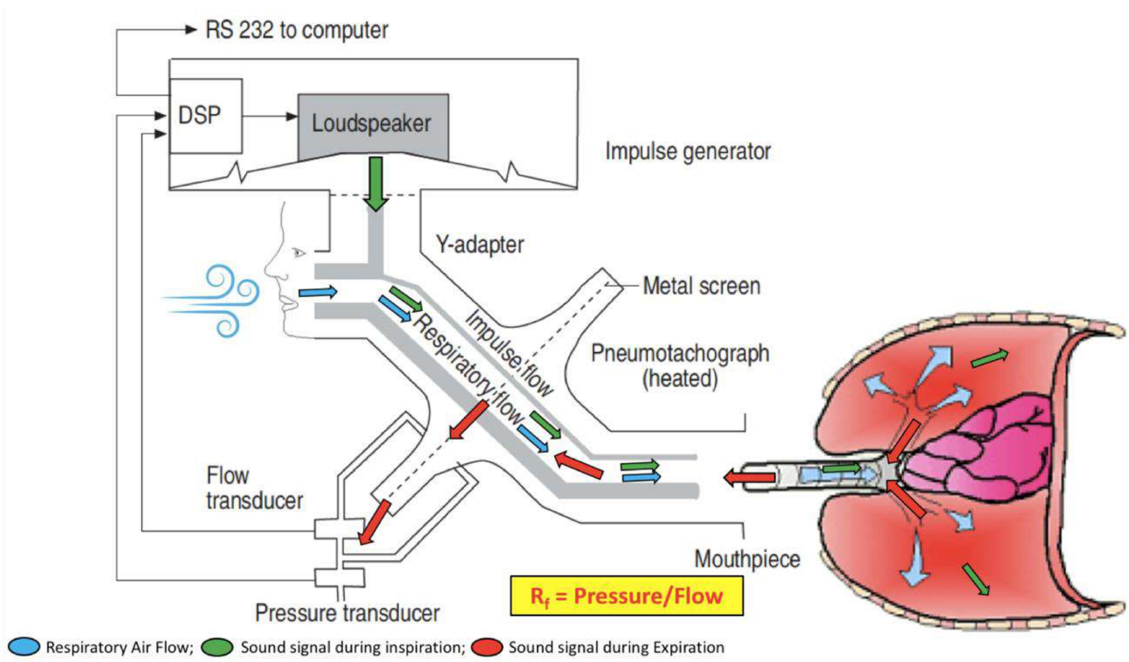


Figure 1 – Schematic diagram depicting superimposition of sound impulses over airflow during FOT

Loud speaker generated impulses (green arrow) travel through airways along with tidal breathing (blue arrow) in the tracheobronchial tree. During expiration, signals are transmitted backwards (red arrow) and are captured by transducers, after signal filtering to dampen the effects of respiratory flow, in order to directly measure flow and pressures on individual frequencies. Later, resistance is calculated by the machine using ohm's law and displayed on the screen.

Mathematical Modelling

The respiratory system is often modelled using simple linear equations that describe the pressure-flow relationship. The model typically involves parameters such as airway resistance (R), tissue compliance (C), and inertance (I), allowing for a detailed assessment of airway and tissue mechanics.

Parameters measured (Figure 2)

- Resistance (Rrs): Reflects the resistive properties of the airways.

- Reactance (Xrs): Represents the combined effects of airway and tissue elasticity/capacitance and inertance. As the force is happening in the opposite direction, Xrs is represented in negative (minus) values from baseline.

- Impedance (Zrs): A complex quantity representing both Rrs and Xrs, often plotted as a function of frequency.

- Resonant frequency (Fres) – It is usually represented as an absolute value of frequency at which (negative) capacitative and (positive) inertial components of Xrs cancels each other and meets at zero line (baseline).

- Reactance Area (Ax) – Reactance area, also called as Goldman's triangle, is the area below baseline (in the negative direction) till X_5 (Reactance at 5 Hz) and on the right side till Fres.

Figure 2 – Common parameters measured during FOT

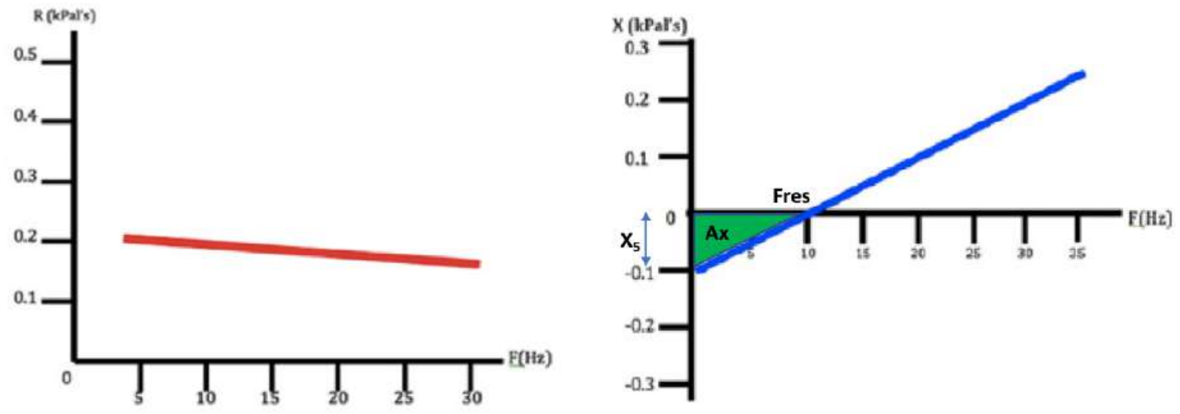


Figure 2 – Common parameters measured during FOT

R – Resistance in kilopascal per litre per second (Red line), F – Frequency in Hertz , Fres – Resonant Frequency, X – Reactance in kilopascal per litre per second (Blue line), X_5 – Reactance at 5 Hz, Ax – Reactance Area (Green zone)

Types of FOT and Waveforms (Figure 3)

In clinical practice, frequency range between 3-41 Hz are commonly used. FOT can be categorized based on the frequencies of oscillations used:

1. Mono/Single/Sinusoidal frequency (Figure 3a, 4a) – Here, single frequencies (5 or 8 or 14 Hz) are used for demonstration of airflow characteristics at a given point of time. As different frequencies can only be used one after another, this technique is time consuming and recommended in special situations only where airway resistance is significantly high.
2. Impulse Oscillometry (IOS) (Figure 3b) – Multiple impulses of fundamental frequency (5 Hz) are used simultaneously mimicking square wave pattern due to overlapping of different sine waves (Figure 4b). Thought IOS reduces test time, but the characteristics of 5 Hz are non-significantly altered due to overlapping of impulses at regular interval. Resistance (Rrs) measured by recurrent impulses is higher than PRN due to impedance distortion.

3. Pseudo Random Noise (PRN) (Figure 3c) – Prime number frequencies (5, 11 and 19 Hz) are used in order to save time without affecting the data characteristics. Non-specific waveform pattern is observed (Figure 4c). If available, PRN is considered better modality than IOS.

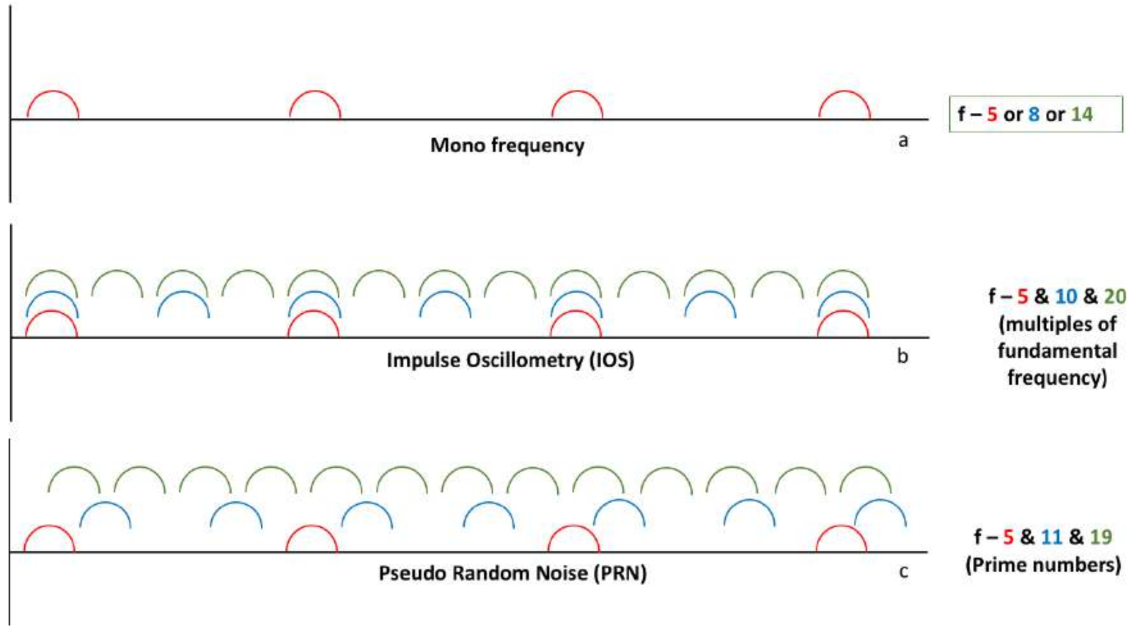


Figure 3 – Types of FOT

f – frequency in Hertz (Hz)

a) Individual frequency sound waves are generated at a time, b) Multiples of fundamental frequency (5 Hz) are transmitted simultaneously with overriding of impulses, c) Frequencies of prime numbers are transmitted simultaneously without any overlap.

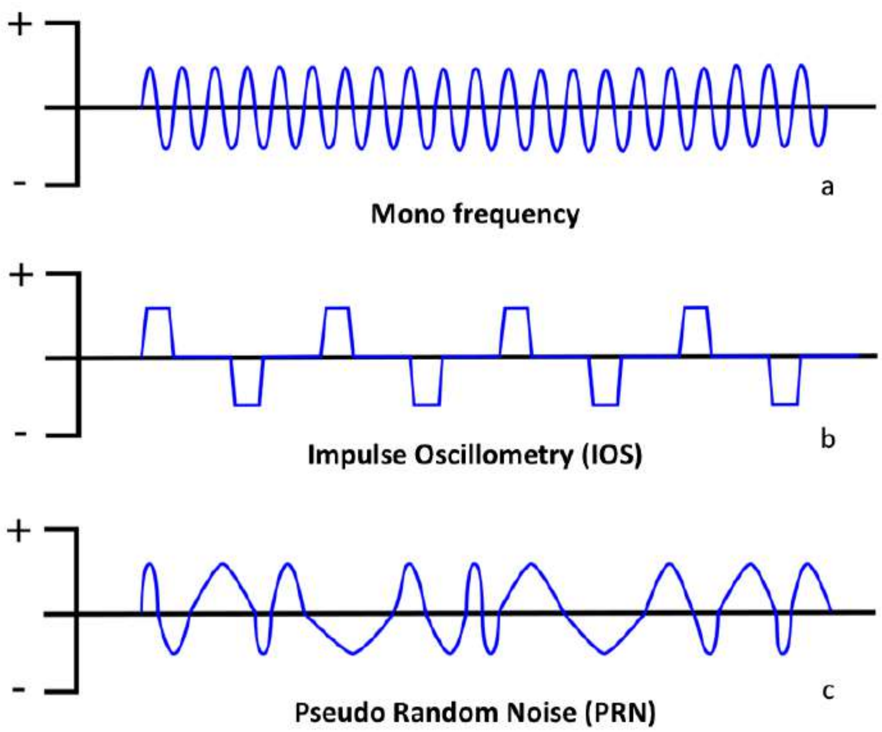


Figure 4 – Types of waveforms in different FOTs

a) Typical sinusoidal waves are generated in mono frequency FOT, b) Square wave pattern is produced due to aggregation of overlapping sinusoidal waves, c) Pseudorandom pattern is produced due to non-overlapping multiple sinusoidal waves in random order generated over prime number frequencies.

Machines and Devices

Several devices are available for FOT, each with varying capabilities and applications (Table 1). These machines typically include advanced software for data acquisition, signal processing, and interpretation. Features like real-time data display, automated quality control, and patient-specific analysis are standard in most modern FOT devices.

Table 1 – Types and frequency contents of available FOT machines

Device	Frequencies (Hz)	Signal type	Recording time
Wave tube	5, 11, 13, 17, 19, 23, 29, 31, 37	Pseudo-random, relative primes	16 s
TremoFlo C-100	5, 11, 13, 17, 19, 23, 29, 31, 37	Pseudo-random, relative primes	16 s
MasterScreen IOS[1]	5, 10, 15, 20, 25, 35	Recurrent impulses	30 s
Most Graph-O2 imp	5, 10, 15, 20, 25, 30, 35	Recurrent impulses	60 s
Most Graph-O2 prn	5, 10, 15, 20, 25, 30, 35	Pseudo-random	60 s
Quark i2m	4, 6, 8, …, 32, 34, 36	Pseudo-random	8 s
Resmon Pro[1]	5, 11, 13, 17, 19, 23, 29, 31, 37	Pseudo-random, relative primes	30 s
Resmon Pro 3f[1]	5, 11, 19	Pseudo-random, relative primes	5 breaths
Pulmoscan[1]	4-32	Pseudo-random	10 breaths
Antlia Pro[1]	5, 10, 14, 20 5, 11, 19	Mono frequency Multi frequency	24 seconds

[1]available in Indian market for clinical use.

Analysis of Waveforms

As frequency is inversely proportional to wavelength, smaller frequency impulses (5 Hz) travels deeper in the airways than larger frequency (19/20 Hz) (Figure 5). Thus, low-frequency oscillations (e.g., 5 Hz) reflects entire airways, while high-frequency oscillations (e.g., 19 or 20 Hz) are more sensitive to large or central airway functions (Figure 5, Table 2). In healthy adults, contribution by smaller airways resistance is practically negligible making it frequency independent, whereas it became significantly higher in young children, even under physiological conditions, and more so during peripheral obstruction like asthma thus making it frequency dependent. The frequency-dependence of resistance and reactance can reveal valuable information about different regions of the lung and the nature of airway obstruction. Coefficient of Variation (CoV) in R_5 values with in consecutive efforts should be a maximum of 10% (in adults) or 15% (in children) (3). Post-bronchodilator reversibility is considered significant if there is reduction in anyone out of R_5, X_5 and Ax by at least 40%, 50% or 80% independently (3). However, recent studies have reported lower cut-off values for significant reversibility (4,5).

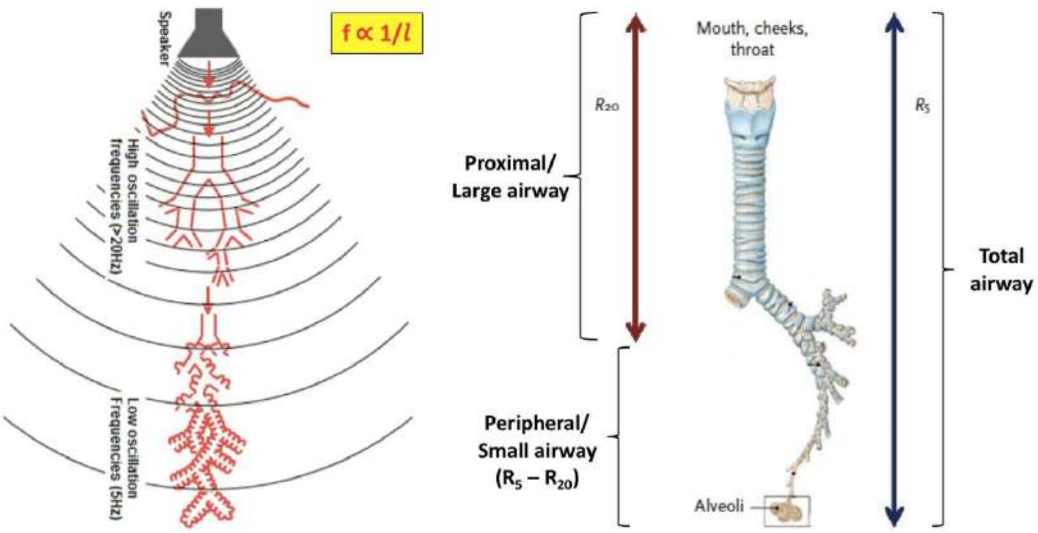
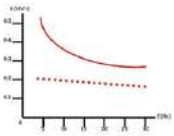
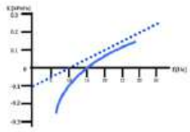
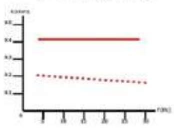
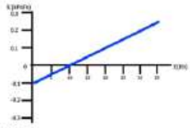
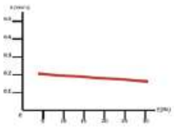
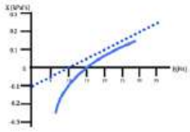


Figure 5 – Different frequencies travelling to varying length of airways

f – frequency, l – length, R_{20} – Resistance at 20 Hz, R_5 – Resistance at 5 Hz reflective of total airway, R_{20} – Resistance at 20 Hz reflective of proximal or large airway, R_5-R_{20} – Reflective of peripheral or small airway resistance

Table 2 – Interpretation of FOT parameters [2]

Pathophysiology	Resistance	R_5	R_{20}	R_5-R_{20}	Reactance	X_5	Fres
Peripheral obstruction		↑↑↑	N/↑	↑↑		More negative	→
Proximal obstruction		↑↑	↑↑	N		N	N
Restrictive lung disease		N	N	N		More negative	→

R_5 – Resistance at 5 Hz, R_{20} – Resistance at 20 Hz, X_5 – Reactance at 5 Hz, Fres – Resonant Frequency, ↑ - Increase, N – Normal, → - Rightward shift

Comparison Against Spirometry

Table 3 enumerates the major differences between two different techniques of measuring pulmonary functions i.e., standard of care ‘Spirometry’ and the current ‘Oscillometry’. FOT, being non-invasive and relatively passive technique, is suitable for children, elderly and those with severe respiratory conditions both at diagnosis and during follow-up. Minimal aerosol generation makes it pandemic safe (Figure 6) compared to conventional spirometry (6). Better sensitivity for restrictive diseases compared to spirometry is another advantage of FOT. However, one needs an expertise to understand and interpret the complex data of FOT in order to utilize for personal care plan of a patient. There is an urgent and unmet need for widespread knowledge dissemination for FOT utility and for creating region-specific normograms. Till then, the changes in baseline parameters in a given situation, either post bronchodilator use or in subsequent follow-up, can guide the clinicians for deciding and titrating therapeutic agents.

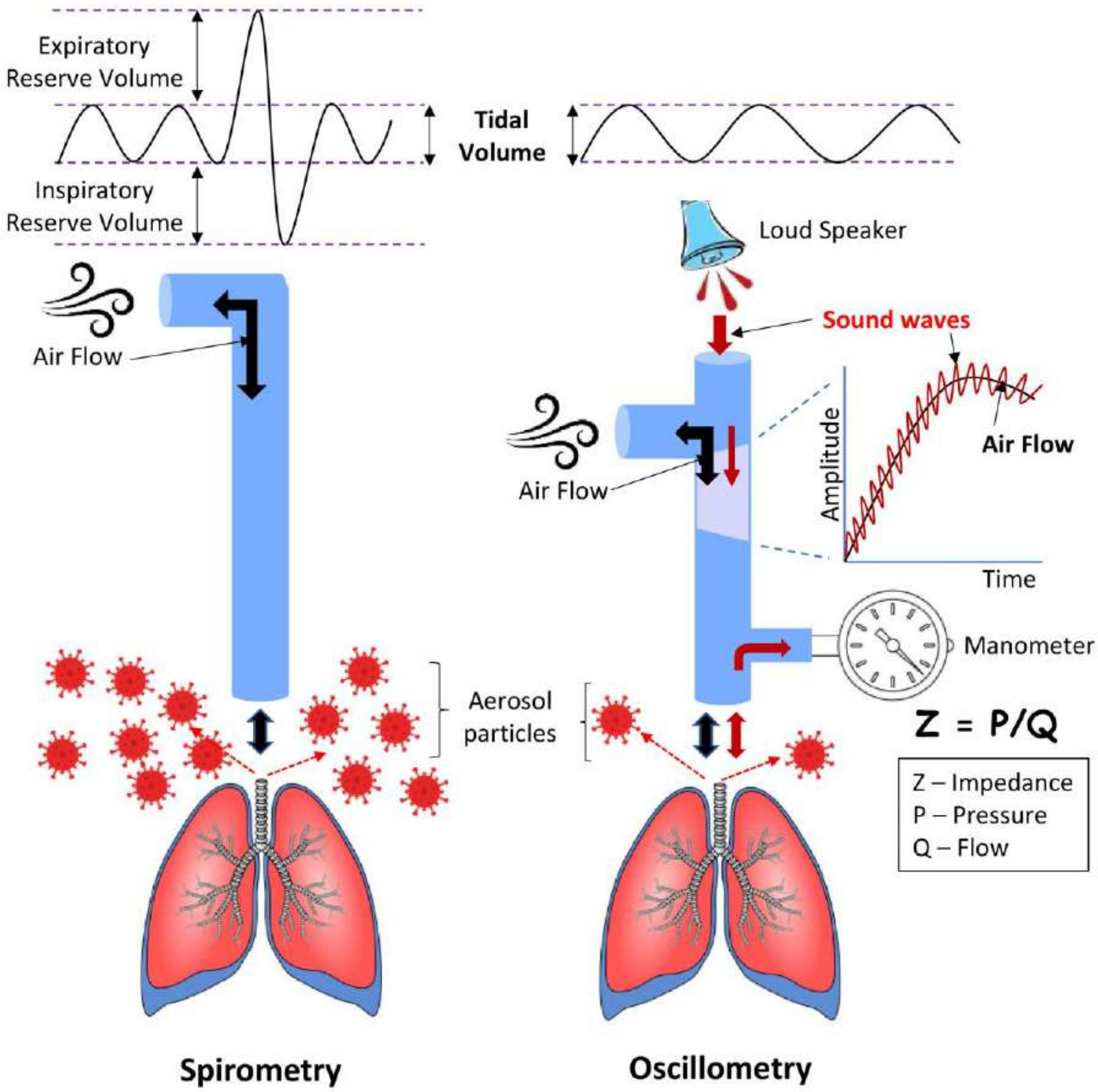
Table 3 – Comparison of Spirometry and Oscillometry

Parameter	**Spirometry**	**Oscillometry**
Principle	Flow rates and lung volumes are considered reflective of airway resistance	Depicts airway resistance at various levels
Parameters measured	FVC, FEV_1, FEF_{25-75}, PEFR	Z, R, X, Fres, Ax
Type of breath required	Forced manoeuvre	Tidal breath
Level of patient cooperation needed	High	Minimal
Can be performed in children	>7 years	>2 years
In patients with neuromuscular weakness, intellectual disability or post cardiothoracic surgery	Procedure cannot be done	Can be done
Sensitivity for detection of peripheral airway dysfunction (obstructive and/or restrictive)	Low	High
Within breath respiratory parameter analysis [7]	Not possible	Possible
Aerosol generation	High	Very low

(Figure 6)		
Standardization of method	Yes	Yet to be done
Reference values	Available for different ethnicities	Need more studies

FVC – Forced Vital Capacity, FEV_1 – Forced Expiratory Volume in 1 second, FEF_{25-75} – Forced Expiratory Flow at 25-75% of FVC, PEFR – Peak Expiratory Flow Rate, Z – Impedance, R – Resistance, X – Reactance, Fres – Resonant frequency, Ax – Reactance area

Figure 6 – Aerosol generation in spirometry versus oscillometry (2)



Aerosol particle generation is much lesser in oscillometry compared to spirometry.

Applications of FOT

(I) Current Applications (8)

- **Pulmonary conditions**
  - **Asthma** – Early detection small airway obstruction is a distinct advantage over spirometry. Reversibility pattern on bronchodilator inhalation is the hallmark of disease (9).
  - **Chronic Obstructive Pulmonary Disease (COPD)** – Maximum effects are seen on Reactance at 5 Hz (X_5) in COPD compared to asthma where Resistance at 5 Hz (R_5) is more affected (10). FOT has earlier been used to monitor therapeutic efficacy of high flow nasal cannula therapy in patients with COPD (11).
  - **Pulmonary fibrosis** – End-inspiratory Reactance (X_I) is more affected than End-expiratory Reactance (X_E) in restrictive lung diseases (12).
  - **Congenital lung malformation** – FOT can be used in children with hypoplastic lungs to determine respiratory functions (13).
- **Extrapulmonary conditions**
  - **Obstructive Sleep Apnea (OSA)** – FOT can be used to determine functional impairment due to airway narrowing during adenoid hypertrophy. It can also help in titrating non-invasive ventilation support by demonstrating effects on airway resistance in real time (14).
  - **Obesity hypoventilation syndrome** – FOT can be a useful tool to demonstrate clinical impacts of obesity on lung mechanics (15). Intra-breath oscillometry can be used to detect tidal expiratory flow limitation and to titrate continuous positive airway pressure (CPAP) therapy (16).

- **Neuro-muscular weakness** – FOT is feasible in patients with poor neuro-muscular reserves like spinomuscular atrophy.
- **Extra-tracheal compression** – Non-reversible central airway obstruction can raise an early alarm for extra-tracheal fixed obstruction.

- **Systemic conditions**
  - **Parkinson's disease** – Respiratory dysfunction in Parkinson's disease by measuring airway tonicity as a marker of cholinergic activity and by monitoring therapeutic efficacy (17).
  - **Spinal-cord injuries** – for functional and structural impairments of pulmonary system (18)
  - **Nephrotic syndrome** – respiratory function monitoring using FOT pre- versus post-diuretic therapy in children with nephrotic syndrome can demonstrate presence of pulmonary edema due to extravascular leakage of fluid (19)
  - **Metabolic syndrome** – effects on pulmonary functions in patients with metabolic syndrome can be monitored by using FOT (20).

(II) Future Applications

The potential future applications of FOT are vast:

- **Allergic Rhinitis (AR)** – Nasal oscillometry can determine nasal resistance which can be useful for demonstration of nasal provocation test in conditions of local AR, determine disease control, demonstrate medication effects and to gauze efficacy of surgery (21).
- Lung function deficits in pre-term children
- Detecting early pulmonary changes in smokers and effects of air pollution
- To identify pulmonary effects of hypoventilation syndromes due to various causes

- Diagnosis of vocal cord dysfunction (22)
- Monitoring of clinical progression in lung and bone marrow transplant
- Titrating level of respiratory support in critical care areas and home monitoring
- **Telemedicine –** Portable FOT devices could facilitate remote monitoring of lung function in patients with chronic respiratory diseases.
- **Personalized Medicine** – Detailed mechanical analysis using FOT could lead to more personalized treatment strategies based on individual lung mechanics.
- **New Biomarkers** – Research into FOT-derived parameters may identify novel biomarkers for respiratory diseases, improving early diagnosis and prognosis.

Drawbacks and Challenges

(I) Technical Challenges

- **Measurement Artefacts** – Movement, swallowing, and airway secretions can introduce artefacts, complicating the interpretation of FOT data. Variable airflow during the manoeuvre will also be responsible for inconsistent results.
- **Calibration Issues** – Accurate calibration of FOT devices is crucial, and discrepancies between machines can lead to inconsistent results.
- **Patient Variability** – Variability in patient anatomy and lung mechanics can affect FOT measurements, making standardization challenging.
- Lack of normograms for different ethnic groups
- Lack of evidence for robust bronchodilator cut-off values
- Absence of uniform grading as per disease severity

(II) Clinical Challenges

- **Limited Awareness** – Many clinicians are unfamiliar with FOT, limiting its widespread adoption.
- **Integration with Existing Workflows** – Incorporating FOT into routine clinical practice requires significant changes to current workflows, including training and investment in new equipment.

Conclusion

The Forced Oscillation Technique represents a valuable tool in the assessment of lung function, offering unique insights into respiratory mechanics that complement traditional spirometry. While FOT has certain limitations, its non-invasive nature, sensitivity to early changes, and ability to assess small airway function make it a promising option in both clinical and research settings. Future advancements in technology and a better understanding of FOT parameters could further expand its role in respiratory medicine, potentially leading to more personalized and effective treatment strategies. At present, FOT can be recommended as a supplementary tool to spirometry in adults whereas it can be a suitable replacement modality in children and indigent (23,24).

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DIAGNOSTIC TESTING FOR CYSTIC FIBROSIS AND PRIMARY CILIARY DYSKINESIA

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Cystic fibrosis (CF) is an autosomal recessive multi-system disorder. The primary defect is dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, that leads to a wide array of clinical presentations. It was thought to be an uncommon disease in India. However, with increasing awareness and availability of diagnostic modalities, a greater number of cases are now being diagnosed. The incidence of cystic fibrosis in Caucasian population is 1:2500 live births whereas it's estimated prevalence in Indian population ranges from 1/43,321 to 1/100,323 (1). Although the prevalence is much lower than the Caucasian population, the clinical profile of CF patients in India is similar to Caucasians and the disease is more severe due to delay in diagnosis, lack of awareness about the disease, and delay in treatment (2). The diagnosis of CF is based on the clinical symptoms and diagnostic tests are needed to confirm it.

Clinical manifestations of CF: The most common clinical manifestations include exocrine pancreatic insufficiency in early life and chronic lung disease. Exocrine pancreatic insufficiency presents as persistent or recurrent oily bulky stools (steatorrhea) and malnutrition, whereas chronic lung disease presents as chronic productive cough, recurrent chest infections including bronchiolitis, airflow obstruction, clubbing and bronchiectasis. Chronic sinusitis and nasal polyposis are commonly associated. Children can also present as hyponatremic salt depletion particularly in the summer months, anemia, hypoproteinemia, edema, rectal prolapse and failure to thrive. In neonates CF can present as meconium ileus, meconium plug, meconium peritonitis, prolonged neonatal jaundice and vitamin K deficiency causing bleeding diathesis. The other less common presentations include intestinal obstruction syndrome (DIOS) and intussusception. Older children and adult patients can present as chronic sinusitis, bronchiectasis, acute or chronic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), cholelithiasis, focal biliary cirrhosis, portal hypertension, insulin dependent hyperglycemia and azoospermia.

Sweat chloride test: Sweat chloride test, first described in 1959 remains the gold standard diagnostic test for CF in an appropriate clinical setting. It comprises three sequential steps: stimulation of sweat production, sweat collection and sweat analysis (3).

Sweat Stimulation: The stimulation of sweat involves using pilocarpine iontophoresis to collect the sweat. The preferred site is the distal flexor surface of either forearm which have the highest concentration of exocrine sweat glands. The intact skin should be properly cleaned before iontophoresis. Appropriate size electrodes are then firmly placed on the patient's limb but should not be overtight. The positive (red) electrode is placed closest to the wrist, but avoiding too close contact with tendons or bone. For safety reasons the negative (black) electrode must always be placed on the same limb as the positive electrode, so the current never crosses the trunk. Filter paper pads or gel discs containing pilocarpine nitrate solution are then placed in contact with the skin at both electrodes and iontophoresis is applied. An electric current is used to carry pilocarpine into the skin of the forearm and locally stimulate the sweat glands.

Sweat Collection: There are two collection methods in use: the capillary tube collection system and the gauze/filter paper method. The capillary tube system (e.g. Macroduct™) is approved and widely used in western countries. Sweat is collected into a disposable capillary tube that contains a blue dye which allows the visualization of the sweat progression. In the second method, sweat is collected onto a pre-weighed chloride-free filter paper or gauze of approximately equal size to the pads used in iontophoresis. During collection, sweat must be protected from contamination and evaporation.

Sweat analysis: Sweat is analyzed to determine the chloride content. For sweat collected on gauze or filter paper, elution step with deionized or distilled water has to be performed. For sweat collected with the capillary tube system, the sweat is expelled slowly out of the capillary system into a PCR tube with a syringe with adapted needle. Three accepted methods for quantitative analysis of sweat chloride include coulometry, Ion Selective Electrode and colorimetry. The other methods such as titration method can be used after validation (4). An indigenous method of sweat collection and titration developed in India has been validated and is cost effective. Sweat conductivity measurements using the Sweat-Check^{TM} analyser have been demonstrated to be as effective. Point of care testing devices have also been developed which can be done bedside (Nanoduct^{TM}) especially in newborns which requires only 3–5μl of sweat (3).

However, in LMIC like ours with high burden of other diseases such as tuberculosis and non-CF bronchiectasis, both the automated sweat testing which comes with a high cost and the filter method which is time consuming are not widely used leading to underdiagnosis of CF.

Sweat test can be performed in neonates aged 2 weeks and above with a minimum weight of 2kg. The minimum quantity of sweat that should be collected for filter paper is 75-100 mg and for capillary tube system is >15microlitre. A sweat chloride value of > 60 mmol/L on two occasions at least one week apart supports the diagnosis of CF when one or more other criteria are present (Table 1). The borderline (or intermediate) values of 30-59 mmol/L have to be confirmed by performing sweat test on one more occasion and further investigations are required. A value of < 30mmol/L makes the diagnosis of CF unlikely.

Certain conditions can give false negative or false positive results. The important conditions that can lead to false positive results include eczema (atopic dermatitis), ectodermal dysplasia, severe malnutrition/failure to thrive/deprivation, endocrine causes like congenital adrenal hyperplasia adrenal insufficiency, hypothyroidism, familial hypoparathyroidism and pseudohypoaldosteronism. Conditions which can give false negative results include dilution of the sample, inadequate sweat collection, edema, dehydration, hypoproteinemia, hyponatremia and CFTR mutations with preserved sweat duct function (5).

Genetic test: There are more than 2000 different CF gene mutations documented. The presence of two pathogenic/likely pathogenic mutations is very supportive of the diagnosis of CF in the appropriate clinical setting. It is difficult to screen all the mutations and most of the laboratories search for the most common mutations within their geographical region which are known to be disease causing. The most common mutation in the Caucasian population is d508 (>70%). Hence customizing mutation panels with most common mutations is relatively easy in European nations. In our country there is wide variation in the mutations and d508 mutation is present in only 20-35% patients (6,7). Therefore, failure to find two CF mutations from a selective or extended panel does not exclude the diagnosis of CF. Genotyping revealing one or two mutations of uncertain clinical consequence without clinical symptoms has no relevance. The genetic analysis is also costly as compared to sweat testing.

Nasal potential difference: Nasal potential difference (PD) can be measured in the mucosa or the inferior turbinates by placing an exploring electrode on the respiratory epithelium and a reference electrode into the subcutaneous tissue of the forearm or an area of abraded skin. Baseline PD is more negative in patients with CF. Depolarization after amiloride and little or no response after the addition isoproterenol increases the diagnostic accuracy (8). Results are influenced by recent viral infections, the presence of rhinitis, the precise anatomic localization of the measuring catheter, as well as polyps and the genotype. Nasal PD is difficult to perform in young children, and there is significant variability in the cut off threshold. This technique is generally confined to research settings.

Table 1: Diagnostic criteria for CF

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary) ***or*** A history of CF in a sibling ***or*** A positive newborn screening test ***plus*** Laboratory evidence for CFTR dysfunction: Two elevated sweat chloride concentrations obtained on separate days ***or*** Identification of two pathogenic/likely pathogenic CF mutations ***or*** An abnormal nasal potential difference measurement

Other supportive tests

Pancreatic function assessment: This can be done by various tests such as 3-day stool collections for fecal fat analysis or fecal elastase 1 to diagnose pancreatic insufficiency. The 72-hour quantitative fecal fat method has been used as an indirect test to diagnose pancreatic insufficiency. If fecal fat excretion is more than 15% of total fat intake in infants less than 6 months of age, and 7% in older infants, then malabsorption is present (5). The major limitation of this test is compliance because it requires a 3- to 5-day stool. Fecal elastase 1 is not influenced by exogenous enzyme administration and had 100% sensitivity and specificity when a value of less than 100 µg/g is used in one study (9). Overall and negative predictive value was 99%. However, it is influenced by presence of intestinal villous atrophy, as in celiac disease, or acute episodes of diarrhea which can lead to falsely low values.

Aquagenic wrinkling test: Aquagenic wrinkling is the wrinkling of hands- on dipping in water for 3min. It has been reported to have a sensitivity of 81% and specificity of 57% for the diagnosis of CF (10).

Radiology: Computed tomography (CT) scanning of the lungs can be used to evaluate subtle pulmonary changes such as bronchial wall thickening, small airway disease, and air trapping not readily visible on plain radiography. CT scan can also be used to evaluate the sinuses, which are invariably opacified in CF patients. In children who are diagnosed late overt bronchiectasis involving the upper lobes initially followed by all the lobes is evident.

Microbiology: Sputum, bronchoalveolar lavage fluid, oropharyngeal swabs, or sinus aspirates can be cultured for known CF pathogens such Staphylococcus aureus (in younger children) or Pseudomonas aeruginosa (in all age groups) may support a possible CF diagnosis.

Pulmonary function tests: Spirometry or multiple breath wash out test where available are valuable tests to detect small airway obstruction.

Newborn screening: The neonatal screening for CF is based on the immunoreactive trypsin assay (IRT) performed on the newborn heel prick sample. IRT concentrations can be raised transiently in healthy newborns, but in newborns with CF, IRT remains raised for weeks to months in both pancreatic sufficient and insufficient CF individuals. A repeat IRT 2 weeks after birth further improves the specificity of the screening. Infants with raised or persistently raised IRT above a locally devised cutoff point should be further tested which may be either a sweat test or a panel of common CFTR mutations for the region performed on the same blood sample or both.

Algorithm: With the advancement in technology, CF is diagnosed at a very early age in western countries. But in LMIC where the resources are limited, an algorithmic approach for the diagnosis of CF has been proposed (Figure 1). The proposed algorithm can be used for the diagnosis of presumptive CF with fair sensitivity and specificity (11).

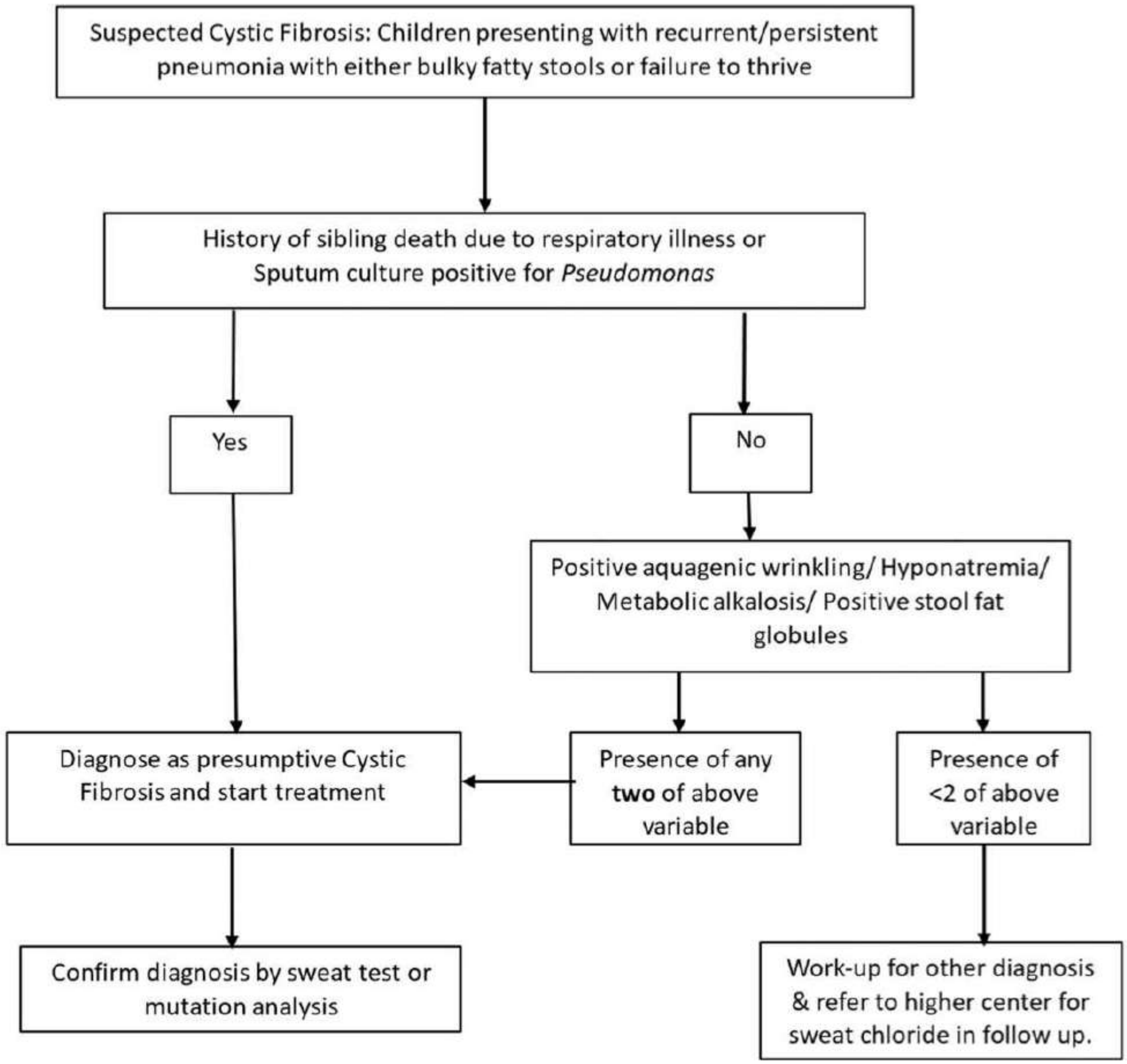

Figure 1: Algorithm for diagnosis of presumptive cystic fibrosis (*Adapted from Sahoo N et al. Development of algorithm for diagnosis of cystic fibrosis in absence of sweat chloride testing in resource-limited setting. Pediatric Pulmonology. 2022; 57: 3077-3083)*

Diagnostic testing for Primary Ciliary Dyskinesia

Primary Ciliary Dyskinesia (PCD) is also a recessively inherited disorder of cilia wherein there is absence of normally functioning cilia. It is characterized by chronic upper and lower airway disease, left-right laterality defects, congenital heart disease and infertility. The clinical picture and age of presentation vary widely. PCD has been considered to be a rare disorder, with an estimated prevalence between 1:20,000 and 1:40,000 (12). The exact prevalence of PCD in India is not known, however PCD has been found to be amongst the commonest causes of non-cystic fibrosis bronchiectasis with approximately 15% of non-CF bronchiectasis patients being suspected to have PCD (13). Indeed, PCD remains largely under-diagnosed in our country owing to the significant overlap of clinical features with other suppurative lung diseases and availability of diagnostic tests only at a few centers. As of now, there is no gold standard diagnostic test and the diagnosis is made by combination of clinical features and variety of investigations as described below. Early diagnosis is imperative for initiating appropriate treatment and preservation of the lung function in a long run.

Clinical features of PCD: PCD affects the entire respiratory tract and patient can present from neonatal period up to adulthood. The symptoms generally begin soon after birth or early childhood but are often nonspecific and hence generally missed. The common symptoms are highlighted in Table 2 (14).

Table 2: Clinical features of Primary Ciliary Dyskinesia

- **Transient tachypnea of Newborn (TTNB)**- Respiratory distress in full term neonate without obvious cause (Prevalence > 75%)
- **Persistent round the year wet cough,** starting early in life (before 6 months of age)
- **Perennial and unabating nasal symptoms**, starting early in life +/- sinusitis (>75%)
- **Recurrent otitis media** (Glue ear) with or without conductive hearing loss (>75%)
- Situs inversus/dextrocardia/heterotaxy (30-75%)
- Unexplained bronchiectasis with childhood onset symptoms (>75%)
- Male infertility with bronchiectasis/nasal symptoms (>75%)
- Sub-fertile female or ectopic pregnancy with respiratory symptoms

The probability of PCD increases if these symptoms are associated with situs inversus or dextrocardia. The examination findings include failure to thrive, clubbing, chronic middle ear effusion, TM perforation/scarring, cholesteatoma, nasal turbinate hypertrophy, mucopurulent discharge, nasal polyps, sinus tenderness, coarse crepitations or airflow limitation and or dextrocardia in 50% of the patients.

The radiographic findings include peribronchial thickening, atelectasis, air-trapping and bronchiectasis typically occurring in the middle and lower lobe. However, these features are non-specific are not diagnostic of PCD.

As mentioned earlier, there is a lack of gold standard test for diagnosing PCD. Therefore, the diagnosis is usually made by composite reference standard using clinical features plus diagnostic tests. The four cardinal features of PCD include early onset year-round wet cough; early-onset year-round nasal congestion; unexplained neonatal respiratory distress and laterality defects (15).

The patients with at least 2 of these features should be further tested as presence of a single feature makes the diagnosis of PCD unlikely. The sensitivity and specificity based on the number of these clinical features present are 37% and 97% if all 4 clinical features are present, 84% and 74% if 3 clinical features are present, 99% and 22% in the presence of 2 clinical features, and 100% and 4% in presence of 1 clinical feature.(12) A diagnostic predictive tool, known as PrImary CiliAry DyskinesiA Rule (PICADAR), has also been developed (Table 3). It has a sensitivity 90% and specificity 75% if the score 5 or more (16).

Table 3: Primary Ciliary Dyskinesia (PICADAR) score

Does the patient have a daily wet cough that started in early childhood?	**Yes – complete PICADAR** **No – STOP. PICADAR**	**Points**
1. Was the patient born pre-term or full term?	Term	2
2. Did the patient experience chest symptoms in the neonatal period (e.g. tachypnoea, cough, pneumonia)?	Yes	2
3. Was the patient admitted to a neonatal unit?	Yes	2
4. Does the patient have a situs abnormality (situs inversus or heterotaxy)?	Yes	4
5. Does the patient have a congenital heart defect?	Yes	2
6. Does the patient have persistent perennial rhinitis?	Yes	1
7. Does the patient experience chronic ear or hearing symptoms (e.g. glue ear, serous otitis media, hearing loss, ear perforation)?	Yes	1
		Total Score-

The main diagnostic tests for PCD include:

1. Nasal Nitric Oxide (nNO)
2. High speed video microscopy analysis (HSVA)
3. Transmission Electron microscopy (TEM) of ciliary biopsy
4. Genetic analysis

Nasal nitric oxide (nNO): Nitric oxide (NO) is produced throughout respiratory tract. The normal NO concentration in the nasal passages is 10–100 times higher than in the lower airways. However, the nasal NO concentration has been found to be consistently low in PCD due to various reasons such as sinus cavity hypoplasia, increased breakdown of NO by bacteria, consumption of NO by bacteria, decreased production of NO, entrapment of NO in obstructed airways and decreased expression of inducible NOS. nNO measurement was considered as a screening test for PCD in previously. However, recent meta-analysis concluded that the diagnostic accuracy of nNO by chemiluminescence technique was excellent in patients with clinical features compatible with PCD and in whom cystic fibrosis had been ruled out (17).

The nNO can be measured by two types of analysers; Chemiluminescence analysers and electromechanical analyser which is a portable device. Velum closure technique by a stationary chemiluminescence analyser is considered the gold standard for nNO measurement and has a sensitivity of 90-100% and specificity of 75-97% (18). However, this technique is difficult to perform in children. Moreover, chemiluminescence analysers are extremely expensive and largely limited to research setting except in European countries. The cut-off for nNO using this method is 77 nl/min. Values less than this are more than 95% sensitive and specific for a diagnosis of PCD on the basis of electron microscopy and/or genetic testing (19).

The another more commonly available and used device is the portable electromechanical analyser. NIOX MINO and VERO are the available devices in our country. This is a portable device consisting of a panel with rechargeable battery which has to be connected to a laptop, nasal Olives, Nasal Filter and a nasal tube (Figure 2)

Figure 2: Niox Vero assembly

Procedure: An appropriate size nasal olive is inserted into one of the patients nostril and the child is asked to breathe through the mouth for 2 minutes. The machine then calculates the nNO in 90 seconds. Although the procedure is simple, it requires some amount of cooperation and hence can be performed in children more than 5-6 years of age. The child should not inhale through the nose during the nasal measurement. nNO measurement should not be performed nasal NO if there is evidence of blood in the nostrils.

The nNO is measured as parts per billion (ppb) by the machine. It has to be converted into nl/min. The formula for conversion is: Nasal NO (nl/min)= ppb x flow rate (L/min). The commonly used flow rates for NIOX MINO and VERO is 5 ml/sec= 0.3 L/min. So if the machine reads 100 ppb on 5 ml/sec, it will be 100 x 0.3= 30 nl/min. The cut-off for portable electrochemical analyzer is 30-40 nL/min. however, different studies have used different methods and cut-off values (20).

Tidal breathing technique or use of portable analyzers are less sensitive and specific but may support the diagnosis of PCD. nNO alone cannot accurately rule in or rule out PCD; but since it is relatively easy to perform and non-invasive it is used as part of the diagnostic work-up of suspected PCD (18).

High-speed video microscopy analysis (HSVA): HSVA is an ex-vivo assessment of ciliary activity of the respiratory epithelium. The cilia in the nasal respiratory epithelium are directly visualized using a light microscope. The ciliary movements are recorded with a high- speed video camera mounted on the microscope. The videos are then analyzed to assess ciliary function in terms of ciliary beat frequency (CBF) and ciliary beat pattern (CBP).

The normal CBF is between 8-14Hz. The abnormalities of CBP include static, slow, rotating, hyper-frequent cilia with an incomplete beat. One can exclude a diagnosis of PCD if both are normal. It is important that the sample should be adequate to accurately determine the CBF and CBP. The adequacy of the sample is determined by a normal edge (intact uniform ciliated epithelial strip >50 μm in length) or a ciliated edge with minor projections. A ciliated edge with major projections or an isolated ciliated cell or singular cells should not be considered for analysis. A sample with a minimum of seven (up to a maximum of 10) normal ciliated epithelial edges is considered adequate and at least three sessions should be performed for each patient. CBP analysis is more sensitive, specific and has higher positive and negative predictive value (21). Hence, CBF should not be used without assessment of ciliary beat pattern in diagnosing PCD (18).

A CBF of < 11Hz and abnormal CBP is suggestive of PCD, CBF ≥11 Hz, but abnormal CBP makes PCD likely, whereas CBF < 11 Hz, but normal CBP and CBF ≥11 Hz and normal CBP make PCD unlikely. HSVA is an accurate test for PCD when performed by experienced observers with adequate sample combining ciliary beat frequency measurement and pattern analysis (sensitivity of 0.95–1.00 and specificity of 0.93–0.95) (18).

The limitations of HSVM are that the technique requires considerable observer expertise, there is limited availability of the equipment in our country, there is lack of quantitative normative data for interpretation of ciliary beat patterns which is highly subjective, viral infections, environmental pollutants, poor sampling and processing can also produce false positive or false negative results and CBF may be lower, normal or increased in PCD depending on the genotype (22,23).

Transmission electron microscopy (TEM): TEM detects the ultrastructure of cilia which is the basic abnormality in patients with PCD. TEM can diagnose up to 70% of PCD cases. The sample for PCD can be obtained by brush biopsy of nasal turbinates or bronchial walls (via bronchoscopy) and further micro processed to visualize the ultrastructure of the cilia. Various abnormalities such as absent outer dynein arm, inner dynein arm, missing central microtubules, dislocation of microtubules, abnormal patterns etc can be directly visualized. The major limitation of TEM is that it is available mainly as a research tool at very few centers in our country. The biopsy yield is variable (60-90%), the sample processing is labor-intensive and expensive and some mutation have normal ciliary ultrastructure (e.g. DNAH11) (24). Similar to HSVM, the results may be confounded by secondary changes in ciliary ultrastructure provoked by infection or pollutants.

The ERS task force recommends the use of TEM as part of the diagnostic work-up of patients suspected of having PCD. However, further diagnostic investigations are warranted in patients with normal ultrastructure if the clinical history is strong as some patients with PCD have apparently normal ultrastructure. In patients with hallmark ciliary ultrastructure defects for PCD further confirmatory diagnostic investigations are not required (18).

Genetic analysis: PCD is mainly an autosomal recessive disorder. The majority of the mutations are loss-of-function mutations. Till date mutations in 52 genes have been identified. Identification of non-ambiguous bi-allelic pathogenic/likely pathogenic mutations in autosomal recessive PCD genes establishes the genetic diagnosis of PCD (18). Some of the genes implicated in PCD include DNAH5, DNAH9, DNAH11, DNAI2, DNAL1, CCDC8, CCDC39, CCDC40, CCDC65, ARMC4, HYDIN, RSPH1, RSPH4A, RSPH9, CCNO, CDKN1C, SPAG1, DNAAF1, DNAAF2, DNAAF3, DNAAF5, and NME1 (25). The recently published data from our country identified 108 unique variants in 40 genes among 67 patients. The common genes involved in definite cases of PCD in Indian patients were LRRC6, DNAH5, CCDC39, and HYDIN (26).

The limitations of genetic analysis include large number of genes with an expanding list, limited availability, high cost, not all genes are tested in commercially available panels and a negative genetic test does not necessarily rule out PCD; detects only 65-70% of PCD cases. Moreover, we frequently encounter reports of Variance of unknown significance (VUS) which does not establish the diagnosis of PCD.

The confirmation of diagnosis of PCD or its exclusion is based on the combination of various clinical and combination of tests. The European Respiratory Society and the American Thoracic Society have given diagnostic algorithms with slight variation as shown in figure 3 and 4 (18,27).

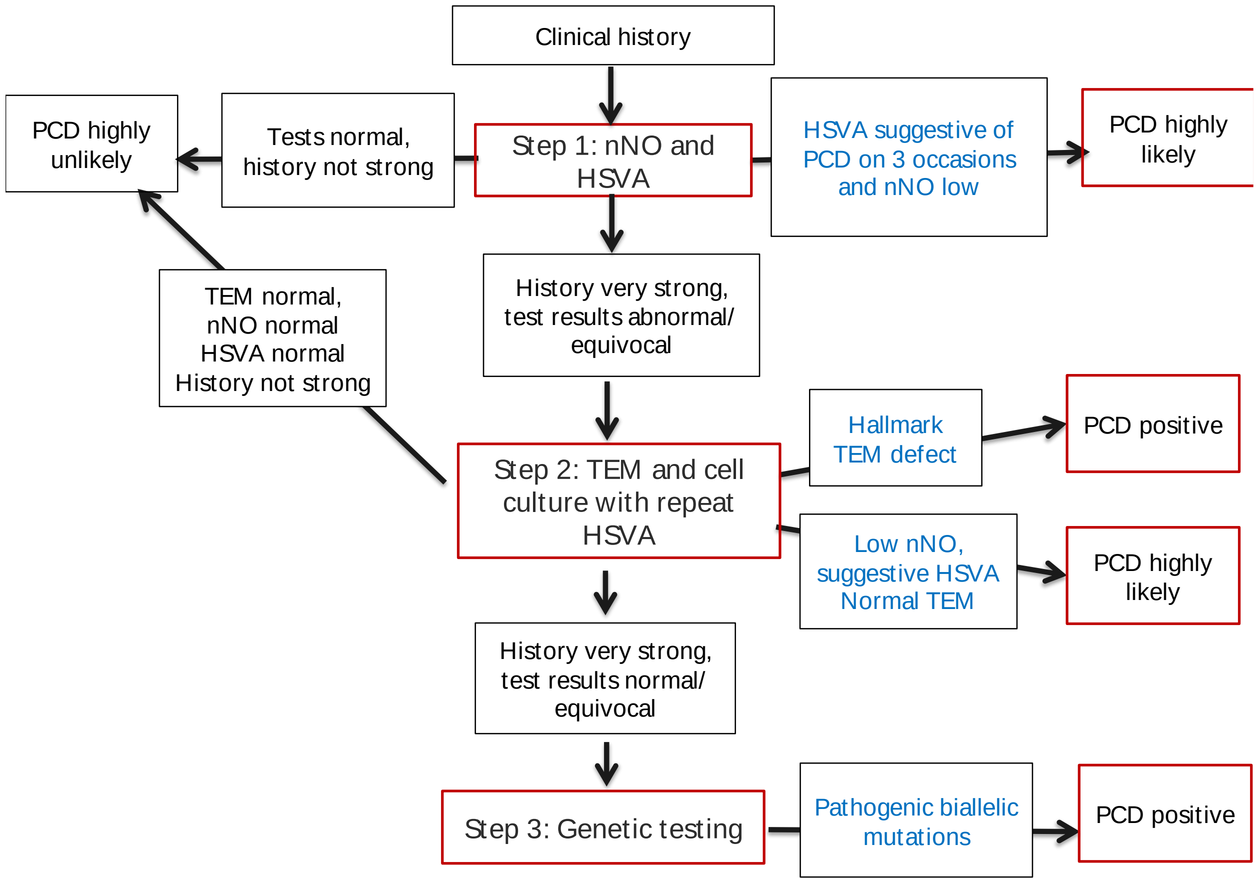

Figure 3: Diagnostic Algorithm for PCD *(Modified from ERS task force, 2017)* (18)

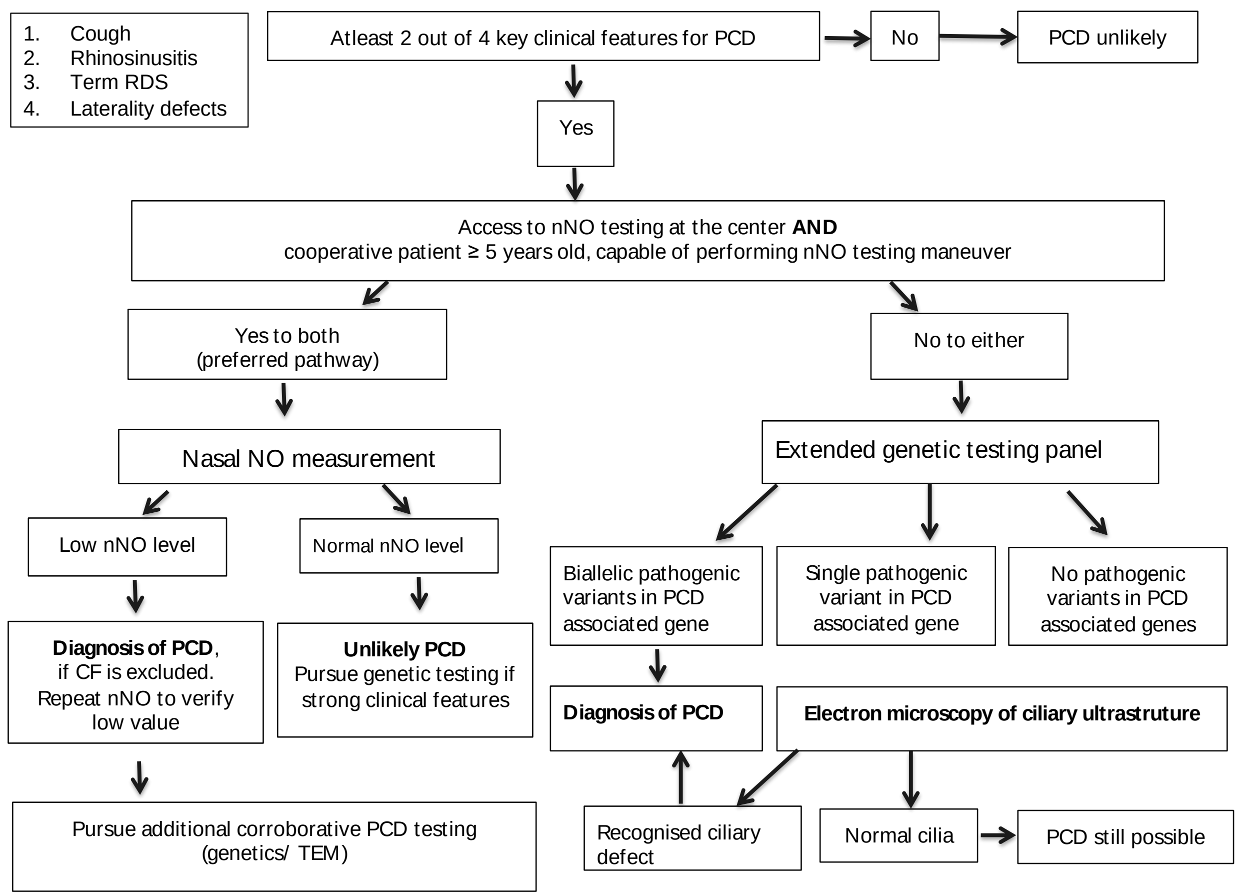

Figure 4: Diagnostic Algorithm for PCD (Modified from American Thoracic society, 2018) (27)

To conclude CF and PCD are relatively underdiagnosed chronic lung diseases due to lack of awareness and unavailability of diagnostic tests at a large scale. Sweat test remains the gold standard test to diagnose CF and should be undertaken promptly whenever this diagnosis is considered. CF remains a clinical diagnosis supported by a functional test of CFTR dysfunction. There is no single gold standard test for diagnosis of PCD and diagnosis is made by combination of clinical features and various tests.

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RADIOLOGY IN PEDIATRIC PULMONOLOGY PRACTICE

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Introduction

Pediatric chest diseases encompass a diverse group of conditions affecting the respiratory system and thoracic structures in children, ranging from neonates to adolescents. These conditions include infectious diseases like pneumonia and bronchiolitis, congenital anomalies such as congenital diaphragmatic hernia and congenital pulmonary airway malformation (CPAM), and chronic conditions like asthma and cystic fibrosis. Additionally, pediatric patients are at risk for neoplastic conditions, including lymphoma and thoracic tumors, as well as inflammatory and autoimmune disorders like interstitial lung disease. The clinical presentation of these diseases often varies with age, complicating diagnosis and management. The dynamic nature of pediatric anatomy and the ongoing development of the thoracic structures necessitate a tailored approach to diagnosis and treatment.

This review aims to provide an overview of pediatric chest diseases, emphasizing the critical role of radiology in their diagnosis and management. It will explore the anatomical and physiological differences in the pediatric chest, the imaging modalities most commonly used, and the challenges associated with interpreting pediatric chest images and recent advancements in imaging technology and their impact on improving diagnostic accuracy and patient outcomes in pediatric chest diseases.

Anatomical and Physiological Considerations

Pediatric thoracic anatomy significantly differs from that of adults, influencing both the presentation of diseases and their radiologic assessment. In children, the thoracic cavity is smaller, with a relatively large thymus gland, particularly in neonates and infants. The ribs are more horizontally oriented, contributing to a barrel-shaped chest in early childhood, which gradually changes as the child grows. The cartilaginous nature of the ribs in children also allows for greater flexibility, impacting the appearance of the chest on imaging. Additionally, the mediastinum and lungs are proportionally larger compared to adults, with the lung parenchyma being less dense and more compliant. These anatomical differences result in distinct radiologic patterns, requiring careful interpretation tailored to pediatric patients.

The pediatric chest undergoes significant growth and development from infancy through adolescence. The lung volume increases dramatically, and the ribs gradually become more oblique, leading to the adult thoracic configuration. Alveolar development continues postnatally, with alveoli increasing in number and size until early adulthood. The size and position of the heart also change, with the heart appearing relatively larger in younger children compared to adults. These developmental changes affect the radiographic appearance of the chest, and normal age-related variations must be recognized to avoid misinterpretation of imaging studies.

The unique anatomical and developmental characteristics of the pediatric chest have critical implications for radiologic imaging. Standard imaging protocols designed for adults are often inappropriate for children, necessitating modifications in technique, positioning, and interpretation. For instance, the presence of a prominent thymus in infants can mimic mediastinal pathology if not properly identified. Additionally, the lower radiodensity of the pediatric lung parenchyma requires adjustments in radiographic exposure to avoid overpenetration. The dynamic changes in chest anatomy during growth demand that radiologists are familiar with normal age-related variations to distinguish them from pathological findings. Consequently, pediatric radiology demands a specialized approach that considers these anatomical and developmental factors to ensure accurate and safe imaging of the pediatric chest.

Imaging Modalities in Pediatric Chest Radiology

Pediatric chest radiology encompasses a range of imaging modalities tailored to the unique anatomical and physiological characteristics of children. The choice of imaging technique depends on the clinical scenario, the age of the patient, and the need to minimize radiation exposure. This review examines the primary imaging modalities used in pediatric chest radiology, including chest X-rays, ultrasonography, magnetic resonance imaging (MRI), contrast-enhanced computed tomography (CECT), and nuclear medicine imaging.

Chest Radiography: Chest radiography (chest X-ray) remains the most commonly utilized imaging modality in pediatric chest radiology due to its accessibility, speed, and relatively low radiation dose. It is often the first-line investigation for a variety of chest conditions, such as pneumonia, asthma, and foreign body aspiration (1). Pediatric chest X-rays require careful technique adjustments to accommodate the smaller size and dynamic nature of pediatric anatomy. Radiologists must be adept at interpreting normal anatomical variants, such as the thymus, which can appear prominent in infants and young children. Despite its widespread use, the two-dimensional nature of chest X-rays limits their ability to provide detailed information about complex or subtle thoracic abnormalities.

Ultrasonography: Ultrasonography (USG) is a valuable imaging tool in pediatric chest radiology, particularly for evaluating the pleura, chest wall, and diaphragmatic abnormalities. Its primary advantage lies in its ability to provide real-time, dynamic imaging without ionizing radiation, making it particularly useful in neonates and infants. USG is highly effective in detecting pleural effusions, consolidations, and diaphragmatic motion abnormalities (2). Additionally, it can be used to guide interventions, such as thoracentesis. However, USG is limited by its operator dependence and the inability to visualize deep intrathoracic structures, particularly in the presence of overlying aerated lung tissue.

Magnetic Resonance Imaging (MRI): MRI is increasingly used in pediatric chest radiology due to its superior soft tissue contrast and the absence of ionizing radiation. It is particularly useful for evaluating mediastinal masses, vascular anomalies, and congenital heart disease. MRI can provide detailed anatomical and functional information, including blood flow and cardiac function assessment through techniques such as phase-contrast imaging (3). The main limitations of MRI include the longer imaging time, the need for sedation in younger children, and limited availability compared to other imaging modalities.

Contrast-Enhanced Computed Tomography: Contrast-Enhanced Computed Tomography (CECT) plays a critical role in the evaluation of complex congenital anomalies, interstitial lung disease, and thoracic tumors in pediatric patients. The high-resolution, cross-sectional images provided by CECT allow for detailed visualization of both lung parenchyma and mediastinal structures. However, the significant radiation dose associated with CECT is a major concern in pediatric patients, necessitating the use of dose reduction strategies, such as low-dose protocols and iterative reconstruction techniques. The administration of intravenous contrast agents further enhances the diagnostic utility of CECT, particularly in evaluating vascular structures and detecting metastatic disease.

Nuclear Medicine Imaging: Nuclear medicine imaging, including positron emission tomography (PET) and single-photon emission computed tomography (SPECT), is less commonly used in pediatric chest radiology but plays a crucial role in specific scenarios, particularly in oncology. PET/CT is valuable for staging and monitoring treatment response in pediatric thoracic malignancies, such as lymphoma. SPECT imaging is used for assessing pulmonary embolism, particularly in cases where CECT is contraindicated. The primary drawback of nuclear medicine imaging is the radiation dose, although advancements in imaging techniques and radiotracer development continue to improve the safety and efficacy of these modalities.

Advanced Imaging Techniques

High-Resolution Computerized Tomography: High-resolution computed tomography (HRCT) is a specialized imaging technique that offers exceptional detail of the lung parenchyma, crucial for evaluating various pediatric chest conditions. Characterized by thin slice acquisition (1-2 mm) and high-resolution algorithms, HRCT provides enhanced spatial resolution, which is vital for accurate diagnosis of diffuse lung diseases and subtle pathological changes. HRCT employs thin collimation and specific imaging protocols designed to optimize spatial resolution while minimizing radiation dose. This is particularly important in pediatric patients, who are more sensitive to ionizing radiation. Advanced techniques, including low-dose CT protocols and automated exposure control, help reduce radiation exposure without compromising diagnostic quality.

HRCT is indicated for assessing conditions such as interstitial lung disease, cystic fibrosis, and bronchopulmonary dysplasia, where it offers detailed visualization of lung structures that are not always evident on conventional CT or X-rays (4). It is also valuable in evaluating congenital anomalies like congenital pulmonary airway malformation (CPAM) and pulmonary sequestration, providing critical anatomical details necessary for surgical planning. The high-resolution images provided by HRCT enable the identification of fine structural changes, such as septal thickening and ground-glass opacities, which are essential for distinguishing between various types of interstitial lung diseases. HRCT also plays a crucial role in monitoring disease progression and evaluating responses to therapy.

Despite its advantages, HRCT is associated with higher radiation doses compared to conventional X-rays, necessitating careful management of imaging protocols to balance diagnostic benefits with radiation risks. In younger patients, sedation may be required to obtain clear images, and interpreting HRCT findings demands specialized expertise.

Dynamic and Functional Imaging: Dynamic and functional imaging plays a crucial role in the evaluation of pediatric chest diseases by providing real-time assessment of lung function and thoracic dynamics. Two key modalities in this context are fluoroscopy and magnetic resonance imaging (MRI), each offering unique advantages for specific clinical scenarios (5).

Fluoroscopy: Fluoroscopy, a form of dynamic X-ray imaging, allows for real-time visualization of chest structures and respiratory movements. In pediatric chest diseases, fluoroscopy is particularly useful for evaluating diaphragmatic function, assessing the movement of the chest wall, and detecting abnormalities such as foreign body aspiration and congenital diaphragmatic hernia. Its ability to provide continuous imaging makes it ideal for observing dynamic processes, such as the movement of the diaphragm during breathing, and for guiding interventions like percutaneous procedures. However, the use of fluoroscopy involves ionizing radiation, which necessitates careful consideration to minimize exposure, especially in pediatric patients.

Magnetic Resonance Imaging: MRI offers a non-invasive approach to functional assessment without ionizing radiation. In pediatric chest diseases, MRI is valuable for evaluating soft tissue structures and assessing dynamic lung function through advanced techniques like phase-contrast imaging. MRI can provide detailed information on airflow dynamics, pulmonary perfusion, and cardiac function, which is particularly beneficial in conditions such as congenital heart disease and complex congenital lung anomalies. The high soft tissue contrast and lack of radiation exposure make MRI a preferred choice for long-term monitoring and functional assessment in children with chronic or recurrent respiratory conditions. However, MRI requires longer scan times and may necessitate sedation for younger patients to ensure compliance.

Thus, dynamic imaging modalities such as fluoroscopy and MRI are essential for comprehensive assessment and management of pediatric chest diseases. Fluoroscopy excels in real-time evaluation of dynamic processes, while MRI provides detailed functional information without radiation. Each modality has its specific applications and limitations, and their judicious use can significantly enhance the diagnostic and therapeutic approach in pediatric respiratory care.

Recent Advances in Pediatric Chest Radiology

Artificial Intelligence and Machine Learning. Recent advances in pediatric chest radiology have increasingly incorporated artificial intelligence (AI) and machine learning (ML) technologies, significantly enhancing diagnostic accuracy and operational efficiency (6). AI and ML algorithms are being developed to assist in interpreting complex imaging data, optimizing diagnostic workflows, and improving patient outcomes.

AI algorithms, particularly those based on deep learning, have shown promising results in detecting and classifying a range of pediatric chest conditions from radiographic images. These include pneumonia, congenital anomalies, and tumors. Machine learning models can analyse vast amounts of imaging data to identify patterns and anomalies that might be subtle or overlooked by human radiologists. This capability aids in early diagnosis, which is crucial for effective treatment and improved prognosis in pediatric patients (7).

Additionally, AI-driven tools are being integrated into radiology workflows to enhance efficiency. Automated image analysis can prioritize cases based on severity, flag abnormal findings for further review, and even assist in quantifying disease progression. These tools not only support radiologists in managing large volumes of cases but also contribute to standardizing interpretations and reducing variability.

Despite these advancements, challenges remain, including the need for large, diverse datasets to train algorithms effectively and the necessity of ensuring that AI tools are validated and integrated into clinical practice without introducing bias. Continuous research and development are essential to refine these technologies and address these challenges.

Hybrid Imaging Techniques. Hybrid imaging techniques in pediatric chest radiology enhance diagnostic precision by combining the strengths of different modalities. These approaches facilitate comprehensive evaluations, improve disease staging and treatment planning, and offer valuable insights into complex pediatric chest conditions.

One prominent example is positron emission tomography-computed tomography (PET-CT), which integrates the metabolic information from PET with the high-resolution anatomical details of CT. This hybrid approach is particularly useful in evaluating pediatric thoracic malignancies, such as lymphoma and neuroblastoma, by providing precise tumor localization, staging, and monitoring of treatment response. Another example is MRI combined with CT or USG (8). MRI offers superior soft tissue contrast and functional information without ionizing radiation, making it ideal for assessing complex congenital anomalies and inflammatory conditions. When combined with CT or ultrasonography, MRI can provide a more comprehensive evaluation of both anatomical and functional aspects of chest diseases, facilitating better treatment planning and follow-up. As technology advances, hybrid imaging is expected to further refine diagnostic and therapeutic strategies in pediatric radiology.

3D Imaging and Printing

3D imaging and printing technologies have revolutionized pediatric chest radiology by providing advanced methods for visualization and intervention. Advanced 3D imaging, including high-resolution CT and MRI, enables the creation of detailed three-dimensional reconstructions of the chest. This approach provides a comprehensive view of complex anatomical structures and pathologies, such as congenital anomalies, tumors, and airway malformations. 3D printing has emerged as a powerful adjunct to 3D imaging, allowing for the physical creation of anatomical models based on imaging data. These models are invaluable for preoperative planning, particularly in complex cases where visualization of the anatomy is critical. Surgeons can use 3D-printed models to practice procedures, plan surgical approaches, and communicate with multidisciplinary teams. Additionally, 3D-printed models can aid in patient and family education by providing a tangible representation of the thoracic pathology. (9)

Conclusion

In summary, pediatric chest diseases cover a wide array of conditions that impact the respiratory system and thoracic structures in children from infancy through adolescence. These include infections, congenital anomalies, chronic conditions, neoplastic disorders, and inflammatory diseases, each presenting unique diagnostic and management challenges due to the dynamic nature of pediatric anatomy and ongoing development.

This review underscores the pivotal role of radiology in diagnosing and managing these conditions. It highlights the necessity for imaging modalities tailored to pediatric patients, including chest X-rays, USG, MRI, CECT, and nuclear medicine imaging. Advanced techniques such as HRCT, dynamic and functional imaging, and hybrid imaging have further refined diagnostic capabilities, though they come with considerations such as radiation dose and the need for specialized expertise.

The integration of artificial intelligence and machine learning in radiology has enhanced diagnostic accuracy and operational efficiency, though challenges related to dataset diversity and algorithm validation remain. Hybrid imaging techniques, such as PET-CT, and 3D imaging and printing technologies have also advanced the field by providing detailed anatomical insights and aiding in preoperative planning and patient education.

Overall, the ongoing advancements in imaging technology and techniques promise to improve diagnostic precision and patient outcomes in pediatric chest radiology, ensuring that children receive optimal care for their chest diseases.

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SYNDROMIC RESPIRATORY PANELS FOR DIAGNOSIS OF RESPIRATORY TRACT INFECTIONS

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Introduction

Respiratory tract infections (RTI) are the commonest cause of seeking healthcare intervention and hospital admissions in children. RTIs place a significant burden on the healthcare system and are the third most common cause of mortality and morbidity, globally (1). Respiratory viruses are the predominant causative agents responsible for most acute respiratory infections both in adults and children (2).

RTIs are extremely common especially in the first year of life. Most of these infections are due to one of the many respiratory viruses, mainly respiratory syncytial virus (RSV), Influenza virus (IV) and Rhinovirus (RV). However, Parainfluenza virus (PIV), Adenovirus (ADV), Human metapneumovirus (hMPV), Bocavirus (BV) and Enterovirus (EV) can also play a relevant role, particularly during epidemics. When bacteria are the cause, *Streptococcus pyogenes* is a common cause of pharyngitis and *Streptococcus pneumoniae* is a typical cause of lower RTIs. In some cases, coinfections with two or more viruses or with viruses and bacteria can occur (3).

The clinical spectrum of the RTIs varies significantly from asymptomatic to mildly symptomatic to potentially fatal disease. The outcomes depend on many factors including the age of the patient, general health status, time of presentation and prompt diagnosis and initiation of appropriate management. Rapidity in diagnostics is required to provide adequate and prompt management to patients (4). The current algorithm for the laboratory diagnosis of

RTIs relies on multiple approaches including gold-standard conventional methods, among which the traditional culture is the most used and innovative ones such as molecular methods, mostly used to detect viruses and atypical bacteria (4).

Routine laboratory-based pathogen tests such as viral culture, immunofluorescence assays, and single-target reverse-transcription polymerase chain reaction (RT-PCR) techniques, do not generally provide results rapidly enough to have an impact on clinical decisions. Rapid antigen detection tests (RADTs) also have been shown to have poor sensitivity in detecting respiratory viruses in adults. Conventional testing may be laborious, comprising multiple complex steps; require special instruments that may challenge the capacity of clinical laboratories; and involve delays due to transit of specimens, batch testing, and time in reporting or authorizing results. Consequences of delays in accurate diagnosis may lead to longer hospital stays and worse health care outcomes (5).

Rapid Multiplex Assay

Rapid multiplex molecular testing platforms allow accurate detection of a wide range of viral pathogens simultaneously. Multiplex testing platforms also may be "sample-to-answer" in design, such that the extraction, amplification, and analysis of specimens are fully integrated within closed processes (e.g., individual cartridges). Rapid multiplex PCR testing with sample-to answer systems provides an opportunity for the accurate detection of multiple respiratory targets with similar presenting symptoms (i.e., syndromic), in under one hour. The potential benefits of rapid multiplex panels include earlier discharge and directed use of antimicrobials and isolation facilities (5).

Some of the examples of FDA-cleared multiplex molecular panels and others for detection of microbial pathogens are given below (6).

1. FilmArray Respiratory Panel (RP and RP2) from BioFire Diagnostics.
2. xTAG Respiratory Viral Panel (RVP) and Respiratory Pathogen Panel (RPP) from Luminex Corp.
3. eSensor RVP and ePlex RPP from GenMark Diagnostic
4. Verigene Respiratory Virus Plus Nucleic Acid Test (RV+ and RP Flex) from Luminex Corp. (Nanosphere)
5. Allplex™ Respiratory Panels from Seegene, South Korea. (Not FDA approved)

Multiplex platforms based on molecular methods can be used only in the hospital, as they require specific equipment and laboratory technicians with considerable knowledge, training, and experience. Moreover, these platforms have a turnaround time that is significantly shorter than that of culture but generally much longer than that of rapid tests as they take some hours to give reliable results. This can be a limitation in the emergency department or in the intensive care unit, where many patients require immediate diagnostic and therapeutic decisions (3).

Multiplex assays are significantly more sensitive and specific compared with rapid immunochromatographic tests and immunofluorescence assays; however, as multiplex assays detect both viable and non-viable viruses and bacteria, they can lead to debatable results. Generally, the presently developed and marketed multiplex assays exhibit comparable performance with regards to sensitivities and specificities, and detection of coinfections (3).

It's well-known fact that viruses can colonize the respiratory tract in normal individuals. Therefore, viruses can be identified in the asymptomatic incubation period without having an actual role in the disease. Both children admitted to the hospital for non-respiratory diseases and healthy children attending day care were shown to be carriers of at least one respiratory virus in ∼30% of cases, although the viral load was generally lower in carriers than in symptomatic subjects. Notably, the rate of asymptomatic colonization varies significantly from virus to virus. The detection of IV, RSV, hMPV, and PIV is generally indicative of disease, as the frequency of asymptomatic carriage of these agents is relatively uncommon. In contrast, the detection of certain other viruses raises many doubts due to the high frequency with which these viruses can be identified in asymptomatic children. Despite the capacity to cause upper and lower RTIs and to trigger asthma and chronic obstructive pulmonary disease exacerbations, RV is the virus that is most frequently found in asymptomatic patients (3).

When multiplex assays are used, the benefits of determining which infectious agent(s) is (are) potentially responsible for an RTI are strongly limited by the low number of drugs that are active against the respiratory targets that are currently available on these diagnostic platforms. Presently, only drugs against influenza virus, RSV and atypical bacteria are licensed. Furthermore, it is debated that these drugs should be used in all the subjects suffering from infections due to sensitive agents. The systematic use of neuraminidase inhibitors is not recommended for all the cases of influenza because influenza is frequently a mild disease, and the advantage of drug administration is limited to a marginal reduction in the disease duration (3)

Popular multiplex assays with the assessed analytes and key features are listed below. There are several such assays available in the market worldwide with only few like BioFire Panels being available in India.

Panel	Analytes	Analytes	Remarks
The BioFire® Respiratory 2.1 (RP2.1) Panel **Sample** **Nasopharyngeal swab**	**VIRUSES** Adenovirus Coronavirus 229E Coronavirus HKU1 Coronavirus NL63 Coronavirus OC43 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Human Metapneumovirus Human Rhino/Enterovirus Influenza A virus Influenza A virus A/H1 Influenza A virus A/H3 Influenza A virus A/H1-2009 Influenza B virus Parainfluenza virus 1 Parainfluenza virus 2 Parainfluenza virus 3 Parainfluenza virus 4 Respiratory syncytial virus	***BACTERIA*** *Bordetella parapertussis* *Bordetella pertussis* *Chlamydia pneumoniae* *Mycoplasma pneumoniae*	Overall, 97.1% sensitivity, 99.3% specificity The BIOFIRE RP2.1 Panel has a positivity rate of 87.2% compared to 30.2% in rapid antigen tests.[2]
BIOFIRE® FILMARRAY® Pneumonia (PN) Panels **Sample** **BAL-like: (including mini-BAL)** **Sputum: (including endotracheal aspirate)**	**VIRUSES** Adenovirus Coronavirus Human metapneumovirus Human rhino/enterovirus Influenza A virus Influenza B virus Parainfluenza virus Respiratory syncytial virus **BACTERIA (SEMI-QUANTITATIVE)** *Acinetobacter calcoaceticus-baumannii complex* *Enterobacter cloacae complex* *Escherichia coli* *Haemophilus influenzae* *Klebsiella aerogenes* *Klebsiella oxytoca*	**ATYPICAL BACTERIA (QUALITATIVE)** *Chlamydia pneumoniae* *Legionella pneumophila* *Mycoplasma pneumonia* **ANTIMICROBIAL RESISTANCE GENES** *Carbapenemases* IMP KPC NDM OXA-48-like VIM *ESBL* CTX-M *Methicillin resistance*	**BAL:** 96.2% sensitivity and 98.3% specificity **Sputum:** 96.3% sensitivity and 97.2% specificity

	Klebsiella pneumoniae *Moraxella catarrhalis* *Proteus spp.* *Pseudomonas aeruginosa* *Serratia marcescens* *Staphylococcus aureus* *Streptococcus agalactiae* *Streptococcus pneumoniae* *Streptococcus pyogenes*	mecA/C and MREJ (MRSA)	
BIOFIRE® SPOTFIRE® Respiratory/Sore Throat (R/ST) Panel **Sample** **Nasopharyngeal or throat swab in transport media**	**VIRUSES:** Adenovirus Coronavirus SARS-CoV-2 Coronavirus (seasonal) Human metapneumovirus Human rhinov/enterovirus Influenza A virus Influenza A virus A/H1-2009 Influenza A virus A/H3 Influenza B virus Parainfluenza virus Respiratory syncytial virus	**BACTERIA:** *Bordetella parapertussis* *Bordetella pertussis* *Chlamydia pneumoniae* *Mycoplasma pneumoniae*	POC test with test to answer time of approx. 15 minutes.
Allplex™ Respiratory Panel 1 **Sample** **Nasopharyngeal swab** **Nasopharyngeal aspirate** **Bronchoalveolar lavage**	Influenza A virus (Flu A) Influenza A-H1 (Flu A-H1) Influenza A-H1pdm09 (Flu A-H1pdm09) Influenza A-H3 (Flu A-H3) Influenza B virus (Flu B) Respiratory syncytial virus A (RSV A) Respiratory syncytial virus B (RSV B)		Sensitivity & specificity of all Allplex TM Respiratory Panel Assays, were 98% and 100%, respectively(8)
Allplex™ Respiratory Panel 2	Adenovirus Enterovirus Metapneumovirus Parainfluenza virus 1		

Sample **Nasopharyngeal swab** **Nasopharyngeal aspirate** **Bronchoalveolar lavage**	Parainfluenza virus 2 Parainfluenza virus 3 Parainfluenza virus 4		
Allplex™ Respiratory Panel 3 **Sample** **Nasopharyngeal swab** **Nasopharyngeal aspirate** **Bronchoalveolar lavage**	Bocavirus 1/2/3/4 Coronavirus 229E Coronavirus NL63 Coronavirus OC43 Human rhinovirus		
Allplex™ Respiratory Panel 4 **Sample** **Nasopharyngeal swab** **Nasopharyngeal aspirate** **Bronchoalveolar lavage** **Sputum**	*Bordetella parapertussis* *Bordetella pertussis* *Chlamydophila pneumoniae* *Haemophilus influenzae* *Legionella pneumophila* *Mycoplasma pneumoniae* *Streptococcus pneumoniae*		

Multiplex platforms for the identification of respiratory viruses and atypical bacteria allow for the identification of most of the infectious agents that cause respiratory infections in infants and children. It is highly likely that these platforms can be particularly important for studies specifically planned to evaluate epidemiology of respiratory pathogens and clinical research. On the contrary, their routine use in pediatric clinical practice remains debatable. They cannot be used in the community where most of the pediatric respiratory diseases are diagnosed. Moreover, they cannot allow to overcome the limitation of the traditional diagnostic tests for respiratory pathogens as they do not differentiate carriage from infection, do not seem to influence therapy as effective drugs are available only for Influenza virus and RSV, and do not seem to significantly impact of the socioeconomic problems strictly related to pediatric respiratory infections. They seem, however, justified in the presence of severe clinical manifestations and in immunocompromised patients for whom specific treatment option can be available, particularly when they can be used simultaneously with platforms that allow identification of antimicrobial resistance to commonly used drugs. It is highly likely that these platforms, particularly those with high sensitivity and specificity and with low turnaround time, will become essential when new drugs effective and safe against most of the respiratory viruses will be available (3)

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TOOLS OF THE TRADE - FLEXIBLE BRONCHOSCOPY IN PEDIATRIC PRACTICE

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Introduction

Pediatric Flexible Bronchoscopy has evolved from a rarely performed, often avoided test (because of the fear of handling pediatric & neonatal airways) and done only in cases of suspected foreign body aspiration to one of the basic work ups done in the recent times for the evaluation of airways. The indications range from diagnostic ones to collecting bronchoalveolar (BAL) samples for drug sensitivity in cases of MDR tuberculosis to the basic monitoring and work up in a case of lung transplant. Not only this, it serves in therapeutics too, for removal of as varied materials as a foreign body, mucus plugs, tracheal dilatation etc. Interventional Pulmonology indeed in pediatrics though in its nascent stage, has opened the door to further treatments & research.

Flexible fiberoptic bronchoscopy (FFB) has indeed become an integral part of pediatric pulmonology, neonatology, critical care, laryngology, cardiothoracic surgery, etc. Even the anesthetists use these instruments.

Indications for flexible bronchoscopy

Flexible bronchoscopy is indicated, rather should be used frequently as a diagnostic as well as therapeutic modality (Table 1).

Table 1: Indications of FFB in PICU/ NICU

Diagnostic	Therapeutic	Urgent Indications
Evaluation of infections	Atelectasis	Obstruction of ETT
Evaluation of upper airways	Placement of endotracheal tube (ETT)	Dislodged ETT
Evaluation of larynx	Difficult intubation	
Evaluation of subglottis	Removal of foreign body	
Evaluation of trachea	Pulmonary toilet	
Evaluation of tracheostomy	Therapeutic correction of abnormalities	
Dynamic evaluation of upper airways	Closure of bronchopleural fistula	
Dynamic evaluation of lower airways	Placement of stents	
Persistent cough	Bronchoalveolar lavage for pulmonary alveolar proteinosis	
Stridor	Instillation of drugs	
Bilateral wheeze	Aspiration of cysts: mediastinal or bronchogenic	
Unilateral wheeze	Hemoptysis	
Immunocompromised patient	Bronchial Thermoplasty	
Role of FFB in tuberculosis	Endoscopy-Assisted Tracheal Intubation and (Selective) Bronchial Intubation	
Aspiration pneumonia	Percutaneous dilatational tracheostomy	
Atelectasis	Dilation of stricture and stenosis: balloon bronchoplasty	
Evaluation after extubation	Intralesional injection: cidofovir, mitomycin, steroid	
Evaluation of VAP		

(A) Diagnostic Applications

Evaluation of infections

Bronchoscopy is commonly used for identifying pathogens in the lower airways by collecting bronchoalveolar lavage (BAL) using a mucus trap (Figure 1).

Figure 1: Romson's Mucus Extractor, GS 5018

Evaluation of upper airways

A thorough evaluation of the airways starts right with the evaluation from the nostril. Conditions like choanal atresia, nasal polyps, nasopharyngeal masses (figure 2a, b), vallecular cyst (figure 3a, b), pharyngocele and adenoids can be diagnosed.

Figure 2 a & b: One-month-old baby presented with recurrent, episodes of severe respiratory distress since birth. FFB revealed Nasopharyngeal masses in (R) & (L) nostrils (as shown by arrows), causing near complete obstruction. CT scan was done to reveal the extent of the lesion and surgical removal was done. Patient became completely asymptomatic following the removal of masses.

Figure 3 a

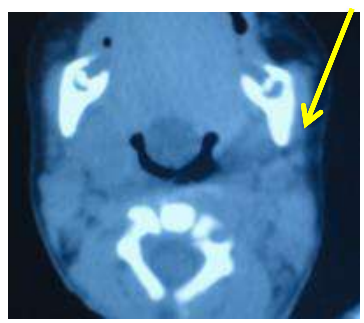


Figure 3 b

Two and half month child presented with recurrent episodes of acute life threatening episodes with increasing frequency of episodes. FFB revealed well-circumscribed cyst (Figure 3a) (as shown by arrow), at the base of the tongue. CT neck was done to define the extent of the cyst (Figure 3b). Surgical excision was done after doing thyroid function tests and thyroid scan which on histopathology was diagnosed as a case of vallecular cyst.

Evaluation of larynx

At the opening of the glottis, it is important to take a pause and observe the movements of the epiglottis, vocal cords and the supraglottic structures. Subglottic foreign bodies (figure 4a) and vocal cord paresis (Figure 4b) and laryngoceles (Figure 5) should be checked.

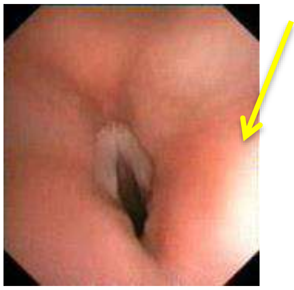


Figure 4a **Figure 4b**

One-year-old child came with the H/O foreign body aspiration the day before (Figure 4 a). Removal was done with rigid bronchoscopy after 6 hours. He was brought with sudden onset stridor, which developed after 3-4 hours of procedure. FFB revealed vocal cord paresis as seen in Figure 4 b (during full expiration).

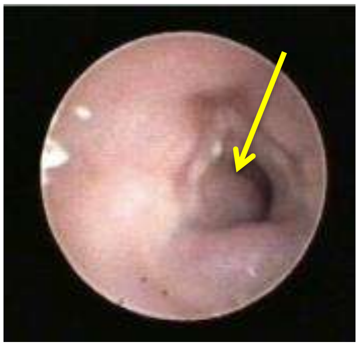


Figure 5: 12-year-old child came with the C/O swelling on the left side of the neck which appeared on talking or blowing and was completely reducible. FFB revealed a laryngocele.

In cases of recurrent croup especially in children below 3 years of age, a low threshold should be maintained for doing bronchoscopy.

In a child presenting with stridor, especially since early infancy, one should suspect laryngomalacia. Evaluation should be done on spontaneous respiration (Figure 6 a & b).

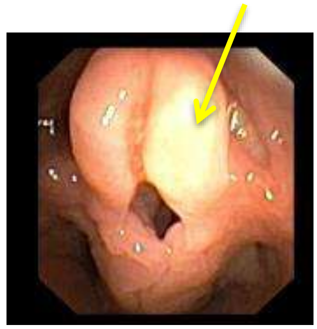


Figure 6 a & b: Two month old baby with stridor since birth. FFB revealed a sigma shaped epiglottis, falling over the glottis suggestive of laryngomalacia.

Evaluation of the subglottis

Subglottis is crucial in cases of pathology in laryngeal area, especially in post-intubation patients. Subglottic stenosis (Figure 7a,b,c), subglottic webs (Figure 8) can be evaluated. Subglottic edema, congestion, mucosal injury, narrowing and granulation formation are the other common abnormalities encountered.

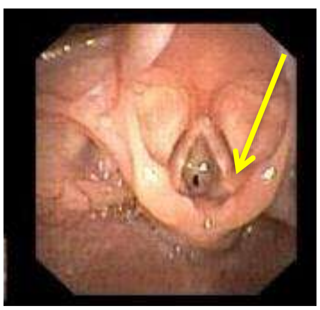


Figure 7a

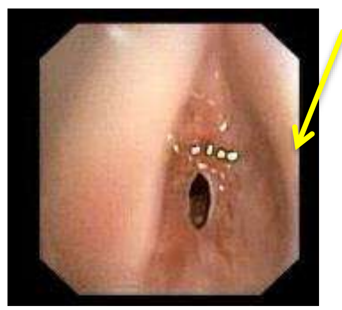


Figure 7b

8 month old child was intubated for acute respiratory failure. After 2 weeks, extubation was done. He immediately developed stridor. Urgent FFB revealed subglottic stenosis (Figure 7 a). Balloon dilatation was done as seen in Figure 7 b

Figure 7 c: The child came back with stridor after a week. FFB revealed recurrence of the subglottic stenosis. Repeat balloon dilatation was done. Child remained asymptomatic in 6 month follow up.

Figure 8: One month old neonate with progressive stridor since birth. FFB revealed a subglottic web.

Evaluation of trachea

Bacterial tracheitis is a life-threatening condition, which requires aggressive management. An urgent bronchoscopy helps to identify the organism and antibiotic selection, also helps in debridement of the mucopurulent secretions & plugs. Figure 9 a,b show tracheal stenosis.

Figure 9 a

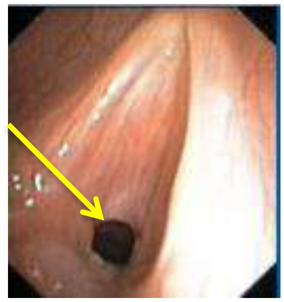


Figure 9 b

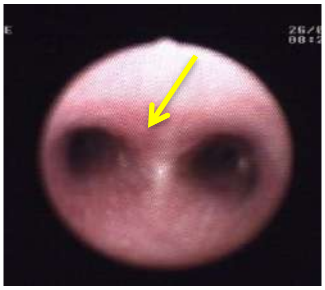
7year old child with recurrent extubation failures. CT Chest revealed tracheal stenosis (Figure 9 a). FFB revealed tracheal stenosis 7 mm long, 7.8 cms from carina (Figure 9 b).

Evaluation of tracheostomy

In a child with tracheostomy, repeated bronchoscopic examinations of the larynx and lower structures is done to evaluate their condition and possible readiness for decannulation.

Dynamic evaluation of airways

Collapse of the walls of trachea and/ or bronchi during expiration is a common acquired abnormality in infants and young children due to bronchomalacia (Figure 10a, b; Figure 11a, b), tracheomalacia (Figure 12a, b) or tracheobronchomalacia.



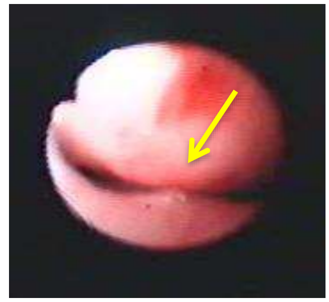


Figure 10 a **Figure10b**

Bronchomalacia in inspiration (figure 10a) and expiration (figure 10b) on spontaneous respiration

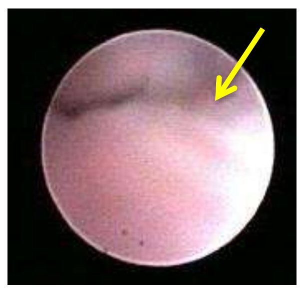


Figure 11 a **Figure 11 b**

4-month-old child presented with stridor. FFB revealed tracheomalacia. Dynamic collapsibility of the trachea seen during inspiration (figure 11 a) and during expiration (figure 11 b)

Figure 12 a

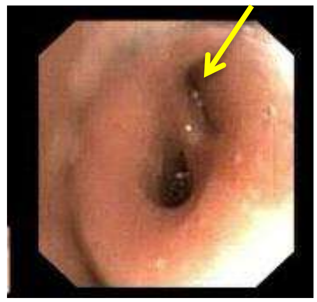


Figure 12 b

5 months old healthy baby with the C/O stridor since birth. On FFB significant bronchomalacia was present as seen in Figure 12 a (inspiration) & 12 b (expiration) while breathing spontaneously.

Persistent cough

Persistent cough is one of the common indications of performing FFB. In a critical care set up, this can be a manifestation of pertussis (presenting as severe spasms of cough), patient of cystic fibrosis requiring ventilation for pneumonia, or a case of forgotten foreign body leading to bronchiectasis (Figure 13 a, b, c, d, e & f) and hypoxemia.

Figure 13 a

Figure 13 b

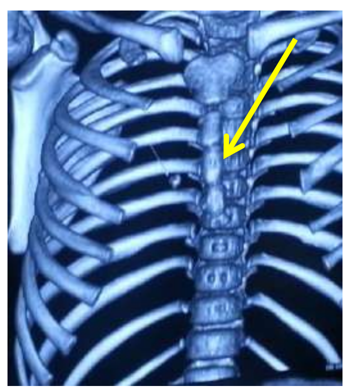


Figure 13 c

7 years old child presented with persistent cough and acute respiratory distress. CXR revealed collapse of right lower lobe. CT Chest showed bronchiectasis of same area with a radio – opaque shadow (Figure 13 a, b, c & d) on 3D reconstruction.

Figure 13 d **Figure 13 e** **Figure 13 f**

FFB revealed a foreign body (old forgotten aspirated foreign body) surrounded with granulation tissue (Figure 13 e, f). Removal was done by Dormia basket.

Stridor

Stridor in children indicates anatomical or functional obstruction of the upper airways. Age of presentation, besides the other clinical features can be a useful diagnostic clue. For example, laryngomalacia is the commonest cause of stridor in early infancy.

Common diagnostic entities in children with stridor (Table 2):

- Congenital malformations of supraglottic, glottic, subglottic structures, trachea.
- Post-extubation edema/ inflammation.
- Severe laryngomalacia, tracheomalacia.
- Tracheo-esophageal cleft.
- Foreign body.
- Vascular ring (e.g., double aortic arch)
- Infections, e.g., retropharyngeal abscess, diphtheria
- Hemangiomas
- Laryngotracheal angioedema
- Tracheomalacia – primary or secondary
- Bronchomalacia – primary or secondary

Table 2: Differential diagnosis in children with stridor

- Tracheomalacia – primary or secondary
- Bronchomalacia – primary or secondary
- Stenosis
  - With complete tracheal rings
  - Without complete tracheal rings
  - Post-traumatic, e.g., post-intubation, post-burns
- Vascular ring compressing the trachea
- Foreign body at carina/ in trachea
- External compression of trachea:
  - Enlarged lymph nodes
  - Cardiac chambers
  - Mediastinal cysts, masses
- Endobronchial tuberculosis, both sides
- Bronchiectasis
- Neoplasms, hemartomas
- Tracheal candidiasis

Table 3: Causes of bilateral wheeze in children

Bilateral wheeze

Besides asthma, the following conditions can result in bilateral wheeze. When there is no response to anti-asthma treatment or there are other clues to the diagnosis (clinical or radiological), flexible bronchoscopy can be a useful tool in the evaluation of such a child (Table 3).

Unilateral wheeze

Unilateral or focal persistent wheeze indicates a localized obstructive pathology. Such a patient is likely to benefit greatly by flexible bronchoscopy in diagnostic evaluation. The causes are as listed (Table 4):

- Foreign body.
- Endobronchial tuberculosis.
- Compression of bronchus from outside by
  - lymph nodes
  - mediastinal mass
  - vascular ring
  - cardiac chambers
- Bronchial stenosis
  - congenital
  - acquired: e.g., post-intubation and vigorous tracheal suction
  - congenital lobar emphysema.

  endobronchial tumor

Table 4: Causes of unilateral wheeze in children.

FFB in immunocompromised child

Detection of opportunistic organisms in the BAL in immunocompromised host (e.g., HIV, anti-malignancy treatment, congenital immunodeficiency disorders) is a very rewarding experience (Figure 14 a, b & c) as it helps in planning the specific treatment.

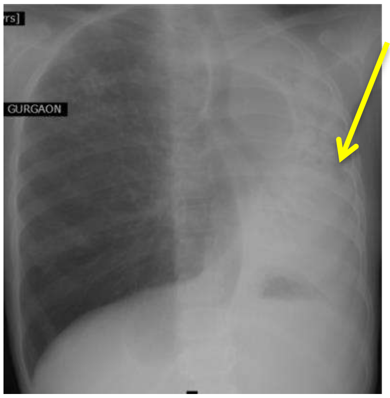


Figure 14 a **Figure 14 b** **Figure 14 c**

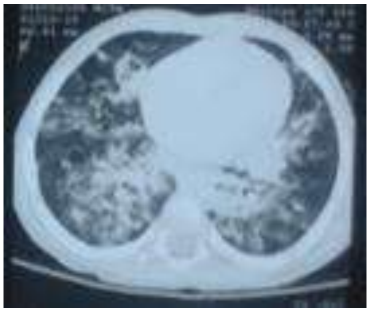
9 years old boy with agammaglobulinemia with left lung collapse (Figure 14 a, b). CT Chest revealed varicose type bronchiectasis of left lung (Figure 14 c). FFB was done to give tracheobronchial toilet. BAL revealed aspergillosis in addition to pseudomonas aeruginosa.

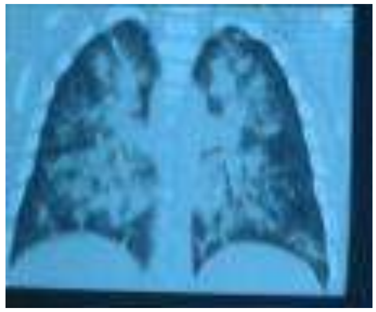
The child with unexplained radiological opacity may be an immediate beneficiary sometimes, when an endobronchial tubercular lesion (Figure 15) is detected or when Mycobacterium tuberculosis is identified on staining and culture.

Figure 15: Caseous material oozing out of lesion of endobronchial tuberculosis

Aspiration pneumonia

Critically ill patients very often have aspiration of gastric contents and oropharyngeal secretions. This results in pneumonia and is significant cause of acute lung injury & acute respiratory distress syndrome.





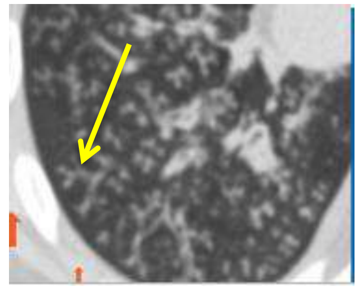


Figure 16a **Figure 16b** **Figure 16c**

7 months old child was air lifted and brought on ventilator after accidental aspiration of cooked dal (lentil soup). CT Chest revealed extensive bronchopneumonia (Figure 16 a & b) and tree in bud appearance (shown by arrow), due to peribronchiolar inflammation (Figure 16 c). FFB was done to give tracheobronchial toilet and BAL revealed pathogen as burkholderia cepacia.

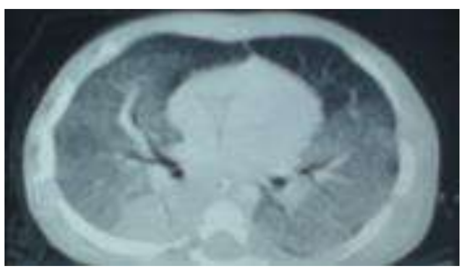


Figure 17 a **Figure 17 b** **Figure 17 c**

1 year old child came with accidental ingestion of approximately 45 cc oil. Child required ventilation for one month. CT Chest showed extensive bronchopneumonia (Figure 17 a & b). Several bronchoalveolar lavages of alternate lungs were done with pre-warmed saline before she could be weaned off oxygen. Lavage fluid would turn opalescent each time (Figure 17 c).

Other causes like tracheo-esophageal cleft, H-type tracheoesophageal fistula etc. can also lead to recurrent aspirations. Techniques for identifying the H-fistula using methylene blue dye have been described.

Figure 18 a

Figure 18 b

Figure 18 c

3 months old child presented with recurrent episodes of ALTE s after oral feeding since 2 weeks. Child had been operated for tracheo – esophageal fistula on day 1 of life. FFB revealed the opening of the fistula (Figure 18 a). Methylene blue injected into the fistula (Figure 18 b & c) was retrieved from the gastric tube immediately thus confirming diagnosis and patency of tract. In Figure 18 c the mouth of fistula is seen to be partially opened due to the injection of the dye.

Atelectasis

Atelectasis of the whole lung, a lobe or a segment is a common condition encountered in the NICU, PICU and the post-operative wards. The causes are listed below (Table 5):

- Extensive mucus plugging
- Surfactant deficiency
- Respiratory muscle weakness
- Mechanical compression of the lung (e.g. development of pleural effusion, pressure from an enlarged liver)
- Mechanical compression of the airways (e.g. compression of the left main stem bronchus by an enlarged heart or vessel)
- Iatrogenic causes such as right (or less commonly left) main stem intubation
- Prolonged immobilization of the patient with subsequent collapse of the dependent regions of the lungs
- Alveolar destruction and collapse

Table 5: Causes of Atelectasis

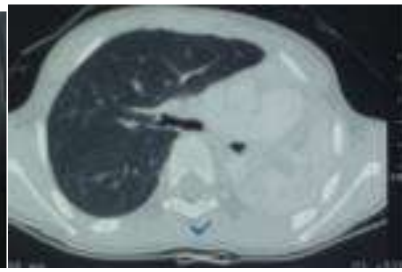
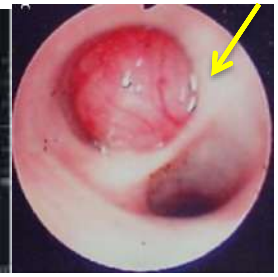
  

Figure 19 a **Figure 19 b** **Figure 19 c**

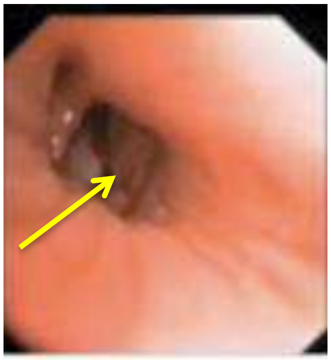
9 years old child presented with persistent cough of 6 months duration and two episodes of hemoptysis. She had received an empirical course of anti tubercular treatment. Chest X Ray showed persistent left lung collapse (Figure 19 a). CT Chest confirmed this finding (Figure 19 b). FFB revealed a mass (Endobronchial leiomyoma on histopathology) completely obliterating the lumen of left main bronchus with atelectasis of the left lung (Figure 19 c).

B. Therapeutic Applications

Therapeutic applications of FFB especially in the context of critically ill patients are:

Persistent or recurrent atelectasis

Atelectasis is one of the most common causes of deterioration &/or delayed recovery of patients in the ICU, especially those on mechanical ventilation. This is often due to mucus plugs or mucopurulent thick secretions or granulations caused by suction catheter/ endotracheal tube trauma.



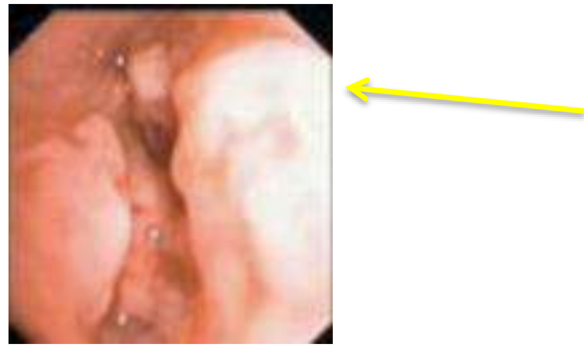


Figure 20 a **Figure 20 b**

2 years old child presented with non resolving pneumonia and respiratory failure. FFB was done which revealed extensive granulations and mucus plugs in the right lower lobe bronchi (Figure 20 a & b). FFB was done six times to remove the granulations and open up the airways and salvage the lung

Placement of the endotracheal tube *(ETT)*

Correct placement of the ETT is not only essential for optimal ventilation, but also to prevent complications such as atelectasis or air leak, when the ET slips into one of the main stem bronchi or hits the carina.

Difficult intubation

When a patient has congenital anatomical abnormality or injury, which prevents or causes incomplete opening of the jaw, bronchoscopic intubation can be done where the ET is threaded over the bronchoscope via Seldinger- type technique.

Drug application

Bronchoscopic administration of surfactant may be an effective and safe alternative in neonates with acute respiratory distress syndrome.

Closure of bronchopleural fistulae

Bronchoscopic management of a bronchopleural fistula with intra-bronchial application of glue (N – butyl cyanoacrylate) is a reasonable alternative to operative closure when the operative risk is great. As the glue should not come into direct contact with the bronchoscope, it should be injected via a catheter placed through the working channel of the instrument. There are very few cases reported in pediatrics (Figure 21 a, b & c).

Figure 21 a

Figure 21 b

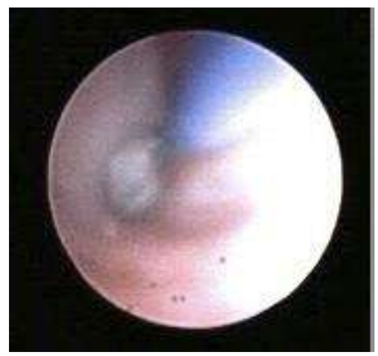


Figure 21 c

2 years old child, case of necrotizing pneumonia, with pyopneumothorax, developed bronchopleural fistula. FFB was done (Figure 21 a) to identify the site of air leak. It was confirmed by instillation of methylene dye (Figure 21 b), which was immediately seen in the intercostal chest tube. Intrabronchial instillation of glue was done (Figure 21 c). The child became asymptomatic immediately and has remained so in 6 weeks follow up.

Removal of foreign body, mucous plug, blood clot

In a suspected case of foreign body aspiration, one needs to do an urgent FFB to confirm the diagnosis and to localize the foreign body. It can be removed by using a Dormia basket or Alligator forceps.

Bronchoalveolar lavage (BAL)

BAL can be defined as the instillation into and recovery from the distal airways of a volume of saline sufficient to ensure that the fluid returned contains at least some fluid that was originally present on the alveolar surface**.** Both soluble and cellular constituents of the alveolar (and small airway) surface fluid are contained in the effluent.

Usually, BAL is done for diagnostic purposes however, there are some therapeutic indications also. Diagnostic indications include persistent / recurrent pulmonary infiltrates, non-resolving pneumonia, immunocompromised host, aspiration pneumonia, suspected pulmonary tuberculosis and child is unable to produce sputum and gastric aspirate is inconclusive, clinical setting of unusual infections like fungal pneumonia, cystic fibrosis, Langerhans cell histiocytosis and lung transplantation. Therapeutic indications for BAL include removal of mucus plugs or blood clots, bronchial casts and lipoid material. Whole lung lavage is required in cases of alveolar proteinosis.

Conclusion

In conclusion, pediatric flexible bronchoscopy has a very important role, both in diagnostics as well as in treatment of respiratory pathologies, and can prove to be a life saving and lung saving procedure, if done at the right time, in the right patient, & in the right setup.

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