UNDERSTANDING THE EARLY, SYSTEMIC PROGRESSION OF CYSTIC FIBROSIS (CF)

A Resource for the CF Center Care Team
(Updated November 2018)
Overview:

CF is a genetic, progressive, multi-systemic disease\textsuperscript{1-5}

- Many symptoms manifest early in life, with signs appearing in utero\textsuperscript{1,4,6}
- Organ damage, such as in the lungs, liver, or pancreas, can occur before symptoms\textsuperscript{4,7,8}
- Techniques to detect CF disease and monitor progression continue to evolve\textsuperscript{9,10}

The role of CFTR dysfunction in cumulative organ damage in CF
CFTR proteins: An important regulator of fluid and ion balance in organs throughout the body

- CFTR proteins are found on epithelial cell surfaces in organs throughout the body\(^1\)\(^-\)\(^4\)
- Normally, CFTR protein channels transport ions, such as chloride and bicarbonate, through the epithelial cell surface in these organs\(^1\)\(^-\)\(^4\)

References:
If the quantity and/or function of CFTR proteins are reduced significantly, the result can be CF

- With too few and/or defective CFTR proteins, the balance of water and salt at epithelial cell surfaces is disrupted\(^1\)\(^-\)\(^4\)\(^-\)\(^6\)
- Mucus becomes thick and sticky in organs throughout the body, and it can clog small passages\(^1\)\(^,\)\(^5\)\(^-\)\(^7\)
  - This interferes with the proper function of the lungs, pancreas, gastrointestinal system, sinuses, liver, and reproductive system

Elevated sweat chloride levels are diagnostic of CF

The sweat gland is a tube-shaped structure in the skin, and has a secretory coil and a reabsorptive duct. 

<table>
<thead>
<tr>
<th>Normal Sweat Gland</th>
<th>CF Sweat Gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Salt</td>
<td>High Salt</td>
</tr>
<tr>
<td>Reabsorptive duct</td>
<td>Reabsorptive duct</td>
</tr>
<tr>
<td>Salt</td>
<td>Salt</td>
</tr>
<tr>
<td>Secretory coil</td>
<td>Secretory coil</td>
</tr>
<tr>
<td>Skin</td>
<td>Skin</td>
</tr>
</tbody>
</table>

Normal sweat contains water and salt (sodium chloride). As fluid passes through the reabsorptive duct, salt is absorbed back into the body. The remaining fluid is emitted onto the skin as sweat.

In CF, the CFTR channel is unable to reabsorb chloride back into the body, resulting in sweat with a high chloride concentration.

### Sweat Chloride Guidelines in the Diagnosis of CF

<table>
<thead>
<tr>
<th>Sweat Chloride Level (mmol/L)</th>
<th>Relation to CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>CF unlikely</td>
</tr>
<tr>
<td>30 to 59</td>
<td>Warrants further diagnostic tests</td>
</tr>
<tr>
<td>≥60</td>
<td>Consistent with CF</td>
</tr>
</tbody>
</table>

Reduced CFTR protein activity begins a cascade leading to structural damage in the lungs

The cascade can result in inflammation, infection, and damage\(^1-5\)

- Progressive lung disease is the leading cause of CF morbidity and mortality\(^2,6\)

A similar cascade occurs in the pancreas, leading to organ damage$^{1,2}$

- Damage to the pancreas is multi-factorial, driven primarily by CFTR dysfunction$^{1,2}$

Lung disease begins early in CF
# Lung disease begins early and progresses throughout the lifetime of a person with CF

## Lung Disease Progression

<table>
<thead>
<tr>
<th></th>
<th>0-5 years</th>
<th>6-10 years</th>
<th>11-20 years</th>
<th>20+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early mucinous plugging and bronchiectasis</td>
<td>Advancing bronchiectasis and pulmonary exacerbations</td>
<td>Bronchiectasis with recurrent exacerbations, requiring nutritional support, supplementary oxygen, and noninvasive ventilator support</td>
<td>Bronchiectasis with hemoptysis, pneumothorax; progressive, respiratory failure; lung transplant</td>
<td></td>
</tr>
</tbody>
</table>

**Additional Considerations**

Potentially irreversible damage as early as 2 years of age; eventually pulmonary insufficiency responsible for ~80% of CF-related deaths

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**References:**
Patients with CF may experience structural lung damage before ppFEV$_1$ declines

**HRCT scans with lung abnormalities in a 13-year-old with a ppFEV$_1$ of 99%**

1. Bronchiectasis
2. Peripheral cysts
3. Bronchiectasis
4. Mucus-plugged bronchus
5. Peripheral cysts

Scans of 13-year-old patient taken from a retrospective study comprised 25 children with CF with a mean age of 10.7 years and a mean ppFEV$_1$ of 76%.$^1$


- Although ppFEV$_1$ is recommended beginning at age 3 years for training purposes and depending on child developmental level, young children frequently have difficulty performing spirometry reliably before the age of 6.$^2$,$^3$
- Patients who can perform spirometry might have lung abnormalities before ppFEV$_1$ declines.$^4$

CT, computed tomography; HRCT, high-resolution computed tomography; ppFEV$_1$, percent predicted forced expiratory volume in 1 second.

Lung disease may also be detected by MRI

The use of MRI in CF continues to evolve

- Historically, MRI has been of limited use in assessing lung disease.\(^1\)
- New MRI research techniques, such as ventilation with hyperpolarized gas, can visualize the location and extent of lung abnormalities as reliably as CT scans, but without the radiation exposure.\(^1,2\)
- However, MRI techniques remain research tools requiring specialized equipment and image acquisition techniques.\(^3\)

Nineteen children with CF and 10 controls were assessed. Subjects attended on a single occasion when clinically stable, and were assessed with SF\(_6\) LCI, plethysmography, spirometry, hyperpolarized \(^3\)He MRI and \(^1\)H MRI. Patients with CF also underwent inspiratory and expiratory chest CT. All subjects had ppFEV\(_1\) z-score > -1.96 and were aged between 6 and 16 years old.\(^2\)

Three patients with CF in whom \(^3\)He MRI detected abnormalities that were not detected in CT scans.\(^2\)

CT, computed tomography; \(^3\)He, hyperpolarized helium-3; \(^1\)H, hydrogen; LCI, lung clearance index; MRI, magnetic resonance imaging; SF\(_6\), sulfur hexafluoride.

Lung clearance index (LCI) may detect early CF airway disease

- LCI is most often used as an endpoint in research trials, especially in young patients to assess lung function. Its clinical use is evolving.
- LCI is more sensitive to small peripheral airway abnormalities than ppFEV$_1$.

**LCI z-score vs CT score**

- LCI shows a significant correlation with CT scan for verification of early disease.
- In the same study, LCI z-score and CT scans revealed pulmonary disease in almost 80% of the study population with normal ppFEV$_1$.

Study evaluated 34 patients with CF and normal ppFEV$_1$, age 6-26 years (mean age 14 years), 26 of whom were found to have early lung disease on CT scan and LCI.

Pancreatic insufficiency and the progression of CF pancreatic disease
Pancreatic insufficiency may be apparent as early as birth and progresses throughout life

<table>
<thead>
<tr>
<th>Pancreatic Insufficiency Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 years</td>
</tr>
<tr>
<td>Pancreatic exocrine insufficiency; up to 71% of patients with CF are pancreatic insufficient at birth(^1,2)</td>
</tr>
<tr>
<td>By 1 year of age, the percent of patients with pancreatic insufficiency rises to approximately 90%(^3)</td>
</tr>
<tr>
<td>6-10 years</td>
</tr>
<tr>
<td>Up to 2% of patients &lt;10 years of age may have CF-related diabetes mellitus(^4)</td>
</tr>
<tr>
<td>11-20 years</td>
</tr>
<tr>
<td>Up to 19% of adolescents have CF-related diabetes mellitus(^4*)</td>
</tr>
<tr>
<td>20+ years</td>
</tr>
<tr>
<td>Up to 40%-50% of adults have CF-related diabetes mellitus(^4)</td>
</tr>
</tbody>
</table>

**Additional Considerations**

- Nutritional/caloric deficiency issue (growth impairment)\(^5\)
- Ongoing pancreatic tissue degradation, as thickened secretions clog more ducts\(^3\)

*Adolescents defined as 10-19 years of age.

CF affects both the exocrine and endocrine functions of the pancreas

• In the healthy pancreas, CFTR channels regulate chloride and bicarbonate secretion, which, in turn, affects the composition of pancreatic fluids that carry enzymes into the intestine\(^1\)
• In CF, these processes are altered due to reduced CFTR protein activity\(^1\)

**Exocrine:** CFTR dysfunction causes clogged pancreatic ducts. Enzymes that digest food are unable to pass into the intestines; therefore, they break down the pancreas itself\(^1,2\)

**Endocrine:** Islet \(\beta\) cells, which regulate insulin secretion, are largely spared early in life, but can be lost over time due to a variety of mechanisms leading to CF-related diabetes\(^1,3\)

Pancreatic exocrine insufficiency is a common early problem in CF

<table>
<thead>
<tr>
<th>CFTR activity(^1) Sweat chloride level(^1)</th>
<th>100 mmol/L</th>
<th>30 mmol/L</th>
<th>&lt;30 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>50%</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pancreatic function(^1)</th>
<th>None</th>
<th>50% pancreatic insufficiency</th>
<th>Normal pancreatic function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical mutations(^1)</td>
<td>F508del G542X G551D</td>
<td>R117H(5T) R334W</td>
<td>Carrier</td>
</tr>
</tbody>
</table>

- Genotypes that result in little to no CFTR activity are typically associated with pancreatic insufficiency\(^1,2\)
- Genotypes that result in at least some CFTR activity are typically associated with pancreatic sufficiency\(^1\)

CF-related diabetes is associated with more severe disease

- Patients with glucose intolerance and poorly controlled CF-related diabetes have lower average ppFEV₁¹,²

Signs of early CF progression may be seen in other organs
### Gastrointestinal complications and symptoms can occur throughout a patient’s lifetime

<table>
<thead>
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<th>Gastrointestinal Complications and Symptoms</th>
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<tbody>
<tr>
<td>0-5 years</td>
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<tr>
<td>Up to 21% of newborns with CF have gastrointestinal problems, such as meconium ileus, within the first days of life&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>6-10 years</td>
</tr>
<tr>
<td>Constant vigilance regarding malnutrition&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>11-20 years</td>
</tr>
<tr>
<td>Decreased motility may lead to chronic constipation&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>20+ years</td>
</tr>
<tr>
<td>Distal intestinal obstruction syndrome (DIOS)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Additional Considerations

- Gastrointestinal abnormalities are often evident before birth<sup>5</sup>

- DIOS may occur in 15% of all patients with CF<sup>6</sup>
- DIOS in older children and adults presents with clinical overlap to meconium ileus seen in newborns<sup>7</sup>
- One study found that 65% of adults with DIOS had meconium ileus as newborns<sup>1</sup>

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**References:**
Sinusitis is common in children and may contribute to lung infections

- Chronic rhinosinusitis is common in children with CF and incidence increases with age\(^1\)
- Overall, sinus disease is found in up to 22% of children with CF\(^1\)


- Sinus infections are difficult to eradicate and can serve as a reservoir for pathogens to repeatedly infect the lungs, although the role of sinuses in the development of chronic lung infection needs further elucidation\(^2,3\)

In the liver, progressive biliary plugging and eventual liver damage can occur

<table>
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<th>Liver Damage Progression</th>
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<td>20+ years</td>
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</table>

- Onset of abnormal liver function tests\(^1\)
- 5% of patients may develop biliary cirrhosis by age 15 years\(^1,2\)
- 5%-10% of patients develop portal hypertension and a liver transplant may be required in some patients (typically age >35 years)\(^1\)

- Reduced or absent CFTR proteins appear to alter bile viscosity and cause mucosal obstruction of bile ducts\(^2,3\)
- Can result in progressive biliary plugging and chronic cholestasis, biliary obstruction, inflammation, and structural damage\(^3\)

CF may impact important regulators of bone metabolism

- CFTR is expressed in bone, and CFTR dysfunction affects bone metabolism\(^1,4\)
- Emergence of bone disease increases as patients get older\(^2\)
- Between the ages of 20 and 35 years, patients with CF may demonstrate arthropathy and CF-related bone disease (osteoporosis)\(^2\)
- Patients with CF are at increased risk of low bone density-related fractures\(^1,3\)
- Nutritional status and chronic inflammation due to other CF-related effects may compound the problem\(^1,3\)

CF can cause fertility problems in both sexes

Males With CF: Lifelong Infertility\textsuperscript{1,2}

- 97% of males with CF have congenital bilateral absence of the vas deferens (CBAVD) and azoospermia\textsuperscript{1}
- CBAVD can occur in men who do not have clinical CF but have a \textit{CFTR} mutation\textsuperscript{1}

Females With CF: Difficulty Conceiving\textsuperscript{3}

- Women can experience fertility impairment related to thick cervical mucus that fails to undergo the usual mid-cycle thinning\textsuperscript{3}

Methods to detect and monitor early CF progression
## Patient growth and nutrition

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination, signs, symptoms</td>
<td>• Useful for all systems: Respiratory, gastrointestinal, liver, etc(^1-^3)</td>
</tr>
<tr>
<td>Growth and nutrition, e.g.:</td>
<td>• Nutritional status is correlated with other clinical parameters, such as</td>
</tr>
<tr>
<td>• Body mass index (BMI)</td>
<td>lung function(^3,^4)</td>
</tr>
<tr>
<td>• Weight-for-length (WFL)</td>
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</tr>
</tbody>
</table>

### Low WFL-BMI percentile before age 6 and ppFEV\(_1\) at ages 6 to 7 years\(^4\)


\(ppFEV_1\), percent predicted forced expiratory volume in 1 second.

### References
# Lung function tests

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| **Spirometry (e.g., ppFEV₁)**           | • Although ppFEV₁ is recommended beginning at age 3 years, young children frequently have difficulty performing spirometry reliably⁴,⁵  
   • ppFEV₁ may not show a decline in lung function despite underlying disease in the lungs³ |
| **Lung Clearance Index (LCI)**          | • Correlates to lung abnormalities detected by imaging more accurately than ppFEV₁ in early stages of disease in young children³,⁴  
   • May be easier to perform in younger patients⁵  
   • Has been used as an endpoint in research trials of young pediatric patients to assess lung function⁵  
   • Clinical use of LCI is evolving⁴ |

ppFEV₁, percent predicted forced expiratory volume in 1 second.

# Lung imaging

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Considerations</th>
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</table>
| **Computed Tomography (CT) Scan** | • Visualizes structure and abnormalities of the lungs\(^1\)  
• More sensitive than ppFEV\(_1\) in detecting early lung disease and monitoring progression\(^1\)  
• Radiation burden with frequent imaging may be a concern\(^1\)                                                                 |
| **Magnetic Resonance Imaging (MRI)** | • Can visualize structure and function of the lungs and other organs\(^3\)  
• Does not use radiation\(^3,4\)  
• Emerging MRI techniques used in research include:  
  − Ventilation MRI of the lungs with hyperpolarized gas\(^4\)  
  − Ultra-short echo time (UTE) sequences\(^3,5\)                                                                 |


ppFEV\(_1\), percent predicted forced expiratory volume in 1 second.

**References:**  
# Lab assessments

## Assessments

<table>
<thead>
<tr>
<th>Liver Function Tests (including ALT, AST, AP, GGT)</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| • Up to 85% of patients with CF may have 2 or more abnormal liver function tests (particularly ALT) by age 21 years<sup>1</sup>  
• CF-related liver disease should be considered if any 2 of the following are present<sup>2</sup>:  
  - Elevated transaminases (AST and ALT) and GGT levels on at least 3 consecutive assessments in 1 year, after excluding other causes  
  - Physical exam, ultrasound, or biopsy suggest liver disease |

<table>
<thead>
<tr>
<th>Exploratory Assessments</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| **Fecal Elastase-1 (FE-1)** | • Measures pancreatic exocrine function<sup>3,4</sup>  
• Low FE-1 after 2 weeks of age signifies pancreatic insufficiency and can help identify pancreatic insufficient patients with inconclusive sweat chloride levels<sup>5,6</sup>  
• Use in clinical trials is currently limited to an exploratory endpoint<sup>7</sup>  
• Assessed from stool samples that are easily obtained from patients of all ages<sup>4</sup> |
| **Immunoreactive Trypsinogen (IRT)** | • Elevations indicate pancreatic damage<sup>8</sup>  
• IRT levels in blood may be raised in infants with CF<sup>8,9</sup>  
• Used in neonatal screening for CF, along with other diagnostic tests, to verify the diagnosis of CF<sup>8,9</sup> |

ALT, alanine transaminase; AST, aspartate transaminase; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

## Additional organ monitoring tests

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Signs and Symptoms (Dysmotility and Constipation)</strong></td>
<td>• Monitoring may help avoid effects that may compound malnourishment due to pancreatic insufficiency¹</td>
</tr>
<tr>
<td><strong>Nasal Endoscopy/CT Radiographic Imaging</strong></td>
<td>• Useful for detecting chronic rhinosinusitis (with or without polyps), which occurs in almost all patients and may precede development of CF lung disease²,³</td>
</tr>
<tr>
<td><strong>Dual-energy x-ray absorptiometry</strong></td>
<td>• Radiation burden may be a concern⁴</td>
</tr>
</tbody>
</table>

CF is a progressive, multi-systemic disease
Signs and symptoms appear early in life

Lung damage begins early—and can go undetected

Pancreatic complications often begin at birth, affecting exocrine function; loss of endocrine function can occur in adulthood

Other organs affected by CF:
- Gastrointestinal
- Sinuses
- Liver
- Reproductive
- Bones

Signs of CF progression can be detected early with established and emerging techniques