UNDERSTANDING HOW CYSTIC FIBROSIS (CF) PROGRESSES
AND ITS IMPACT ON YOUR PATIENTS
CF IS A MULTI-ORGAN, PROGRESSIVE, GENETIC DISEASE

Many problems with CF may be present at birth and persist and progress throughout the patient’s life

<table>
<thead>
<tr>
<th>Age 0-5 years</th>
<th>Lungs</th>
<th>Pancreas</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early mucinous plugging and bronchiectasis¹</td>
<td>Pancreatic exocrine insufficiency; up to 71% of patients with CF are pancreatic insufficient at birth¹,²</td>
<td>Abnormal liver function test results¹</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 6-10 years</th>
<th>Lungs</th>
<th>Pancreas</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing bronchiectasis and pulmonary exacerbations²</td>
<td>Ongoing degradation, as thickened secretions clog more ducts³</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 11-20 years</th>
<th>Lungs</th>
<th>Pancreas</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis with recurrent exacerbations, requiring nutritional support, supplementary oxygen, and noninvasive ventilatory support¹</td>
<td>CF-related diabetes mellitus in approximately 25% of adolescents⁴</td>
<td>Cirrhosis¹</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Age 20+ years</th>
<th>Lungs</th>
<th>Pancreas</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis with hemoptysis, pneumothorax; progressive respiratory failure; lung transplant¹</td>
<td>CF-related diabetes mellitus in up to 40% of adults¹</td>
<td>Portal hypertension (5%-10%); liver transplant¹</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Additional Considerations</th>
<th>Lungs</th>
<th>Pancreas</th>
<th>Liver</th>
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<tr>
<td>Potentially irreversible damage as early as 2 months of age; eventual pulmonary insufficiency responsible for ~80% of CF-related deaths³</td>
<td>Nutritional/caloric deficiency issue (growth impairment)⁵</td>
<td>CF can be associated with biliary cirrhosis (&lt;10%¹)</td>
<td></td>
</tr>
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</table>

Not all patients with CF experience all these symptoms or follow this timeline.
Many problems with CF may be present at birth and persist and progress throughout the patient’s life.

<table>
<thead>
<tr>
<th>Age 0-5 years</th>
<th>Gastrointestinal</th>
<th>Other Symptoms</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Meconium ileus(^1)</td>
<td>Chronic rhinosinusitis; nasal polyp; absence of vas deferens(^{1,3})</td>
</tr>
<tr>
<td>Age 6-10 years</td>
<td>Constant vigilance regarding malnutrition(^3)</td>
<td></td>
</tr>
<tr>
<td>Age 11-20 years</td>
<td>Decreased motility may lead to chronic constipation(^3)</td>
<td>Arthopathy; CF-related bone disease (osteoporosis); female infertility(^{1,6})</td>
</tr>
<tr>
<td>Age 20+ years</td>
<td>Distal intestinal obstruction syndrome(^1)</td>
<td></td>
</tr>
<tr>
<td>Additional Considerations</td>
<td>Gastrointestinal abnormalities often evident before birth(^2)</td>
<td>Potential for renal dysfunction in diabetic patients(^1)</td>
</tr>
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Not all patients with CF experience all these symptoms or follow this timeline.
EVERYONE WITH CF FACES PROGRESSION AND PROGRESSION SHORTENS LIVES

Some genotypes are associated with longer survival than others, but CF remains a life-shortening disease

MORTALITY BY CFTR GENOTYPE CLASSIFICATION

- Age of onset and rate of CF progression vary between and within the genetic mutations known to cause CF
- However, the range of systemic effects and eventual progression is typically similar across all CF-causing genotypes
- In a separate analysis of registry data, the median age of death in people with CF was approximately 29 years

Patients were grouped by genotype, classified as high risk or lower risk of early lung function decline based on the primary functional class of their CFTR mutations, or unclassified if 1 or both alleles were unidentified.

CFTR, cystic fibrosis transmembrane conductance regulator.

Adapted from McKone et al.
Maintaining water and salt balance at the epithelial cell surface requires an adequate quantity and function of CFTR proteins\textsuperscript{10,11}

- CFTR proteins are an important regulator of fluid and ion balance in epithelial tissues in organs throughout the body\textsuperscript{3,10,12,13}
- Normally, CFTR protein channels transport ions, such as chloride and bicarbonate, through the epithelial cell surface in these organs\textsuperscript{3,10,12,13}
  - In normal cells, CFTR proteins are open about 40% of the time\textsuperscript{14}
- This controlled movement of ions helps to regulate water and electrolyte (salt) balance at the cell surface to keep mucus thin and watery\textsuperscript{3,10,12,13}
  - Thin, watery mucus is easily moved through organ passages and helps ensure normal organ function
CF IS CAUSED BY DEFECTIVE OR A REDUCED QUANTITY OF CFTR PROTEINS RESULTING FROM MUTATIONS IN THE CFTR GENE

- 281 known CFTR mutations can result in CF due to too few and/or defective CFTR\(^8,10,15\)

- With too few and/or defective CFTR proteins, water and salt balance at epithelial cell surfaces is disrupted\(^3,6,10,16\)

- Mucus becomes thick and sticky in organs throughout the body, and it can clog small passages\(^3,6,10,16\)
  - This interferes with the proper function of the lungs, pancreas, gastrointestinal system, sinuses, liver, and reproductive system

- This can lead to potentially irreversible lung damage even before loss of function is detected by spirometry\(^1,3,17,18\)
  - Damage can be cumulative over time

\textit{A defect in quantity and/or function of CFTR is the underlying cause of CF}\(^8,19\)
CF-CAUSING CFTR MUTATIONS CAN REDUCE TOTAL CFTR ACTIVITY TO VARYING DEGREES

It depends on how the mutations affect the quantity and/or function of CFTR proteins.

**LITTLE TO NO QUANTITY**

*CFTR protein* → *Cell surface*

**LITTLE TO NO FUNCTION**

*Cell surface* → *CFTR protein*

With little to no CFTR activity, CF appears early and progresses rapidly\(^{10,20-22}\)

**SOME QUANTITY**

*Cell surface* → *Normal CFTR protein*

**SOME FUNCTION**

*Cell surface* → *Abnormal CFTR protein*

With some CFTR activity, CF can appear later in life, but remains progressive\(^{10,20}\)

Regardless of whether they have only some or little to no CFTR activity, people with 2 CF-causing mutations experience progressive CF disease\(^7\)
The cascade of CF in the lungs can result in inflammation, infection, and lung damage, even before loss of lung function is detected by spirometry\textsuperscript{1,3,23,24}.
A SIMILAR CASCADE OF EFFECTS OCCURS IN OTHER ORGAN SYSTEMS

- This cascade results in thickening of secretions, blocking of small passages, inflammation, and organ damage\textsuperscript{3,6,10,16}

- As a consequence, CFTR protein dysfunction affects multiple organ systems with progressive signs and symptoms\textsuperscript{1,3,25-27}
PATIENTS MAY EXPERIENCE STRUCTURAL LUNG DAMAGE BEFORE A DECLINE IN FEV\textsubscript{1} IS DETECTED

HRCT scan shows pulmonary abnormalities in the lungs of a 13-year-old boy with normal pulmonary function tests and a ppFEV\textsubscript{1} of 99\%\textsuperscript{28}

![HRCT images showing pulmonary abnormalities](image)

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

This was a retrospective study in 25 children with CF with a mean age of 10.7 years and a mean FEV\textsubscript{1} of 76. The purpose of the study was to show correlation of CT score with pulmonary disease. The study was able to show correlation of CT score with pulmonary function tests. The image above was the only instance where CT scan was shown to be more sensitive\textsuperscript{28}

CT, computed tomography; FEV\textsubscript{1}, forced expiratory volume in 1 second; HRCT, high-resolution computed tomography; ppFEV\textsubscript{1}, percent predicted FEV\textsubscript{1}.

Adapted from de Jong et al.
PULMONARY EXACERBATIONS ARE A HARMFUL FEATURE OF CF AND CONTRIBUTE TO LUNG DAMAGE

Pulmonary exacerbations begin early in life and increase in incidence with age $^{29,30}$

- Damaging pulmonary exacerbations can occur early in life $^{30}$
  - Although the incidence of exacerbations is relatively low in young children with CF, it increases as the children age $^{29,30}$
  - By age 12 years, as many as 30% of patients will have at least 1 pulmonary exacerbation per year $^{9*}$

- Pulmonary exacerbations are a major cause of irreversible lung damage and can have devastating effects, including increased risk of mortality, hospitalizations, and use of intravenous antibiotics; reduced quality of life; and a rapid decline in pulmonary function $^{9,31}$

*Source of data: Patients with CF treated at Cystic Fibrosis Foundation (CFF)–accredited care centers in the US who consented to have their data entered in 2015 in the CFF Registry.
POOR NUTRITION IN YOUNGER CHILDREN IS CORRELATED WITH REDUCED LUNG FUNCTION

Nutritional deficits due to CF-related pancreatic and digestive problems are associated with decreased lung function

- When young children are below weight for their age, there is a correlation with reduced future lung function.
- In a study of preschool children, it was found that low weight for age at age 3 was associated with a lower ppFEV$_1$ at age 6.

MEAN ppFEV$_1$ AT AGE 6 BY WFA PERCENTILE AT AGE 3 (N=931) 

Adapted from Konstan et al.
WFA, weight for age.
As advances in detection and management have emerged, median predicted survival has increased from approximately 6 months in 1938 to 42 years in 2015\textsuperscript{6,9,33,34}.

**MILESTONES IN THE MANAGEMENT OF CF**

- Pancreatic enzyme replacement therapy
- Sweat test developed
- Antibiotics for CF pathogens
- Airway clearance
- CF center care

- 1940
- 1950
- 1960
- 1970
- 1980

- Tobramycin inhalation solution
- Dornase alpha
- Azithromycin
- Hypertonic saline
- Aztreonam solution for inhalation
- CFTR modulation

- 1990
- 2000
- 2010
- Present
A wide range of tests can help assess CF progression across organ systems

Consideration should be given to a method’s effectiveness, age-based ease of use, and impact/burden on the patient

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<th>Commonly Used Assessment Tools</th>
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<th>Pancreas</th>
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<td>Imaging with HRCT</td>
<td>Spirometry (eg, FEV\textsubscript{1}, FVC)</td>
<td>Magnetic resonance imaging</td>
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<td>Radiation burden with frequent imaging may be a concern, especially in young children\textsuperscript{35}</td>
<td>Standard assessment of lung function, specifically large airways\textsuperscript{5}</td>
<td>Relatively new technology; unproven in clinical practice\textsuperscript{38}</td>
<td>Can detect underlying small airway lung damage even with normal FEV\textsubscript{1}\textsuperscript{5,39}</td>
<td>Standard assessment for the nutritional impact of CF, along with weight and height measurements\textsuperscript{5}</td>
<td>Increasingly used in neonatal screening for CF\textsuperscript{42,43}</td>
<td>Easy to use for all ages\textsuperscript{44}</td>
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FVC, forced vital capacity.
A WIDE RANGE OF TESTS CAN HELP ASSESS CF PROGRESSION ACROSS ORGAN SYSTEMS (cont)

Consideration should be given to a method’s effectiveness, age-based ease of use, and impact/burden on the patient

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<th>Gastrointestinal</th>
<th>Sinus</th>
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<td>Transaminase levels</td>
<td>Signs and symptoms (dysmotility, constipation, etc)</td>
<td>Nasal endoscopy</td>
<td>CT radiographic imaging</td>
<td>Dual-energy x-ray absorptiometry</td>
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Considerations

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<td>Transaminases vary over time in patients with CF-related liver disease. Consistently high transaminase levels occur only with advanced liver disease. Monitoring may help avoid effects that may compound malnourishment due to pancreatic insufficiency. Useful for detecting chronic rhinosinusitis and polyps, which occur in almost all patients and may precede development of CF lung disease. Radiation burden may be a concern.</td>
<td>Monitoring may help avoid effects that may compound malnourishment due to pancreatic insufficiency.</td>
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45, 46, 47, 48, 49, 50, 51
CF PROGRESSION: UNDERSTANDING THE CAUSE AND ITS IMPACT ON YOUR PATIENTS

- CF is a multi-organ, progressive, genetic disease that affects the whole body, and many problems with CF may be present at birth\(^1,^{10}\)
  - Onset and progression of CF symptoms can occur in different organs at different ages

- Multisystemic damage often occurs before symptoms emerge\(^52\)

- Our ability to detect and monitor CF progression in different organs has increased over time with improved understanding of the disease\(^33\)

- All patients with CF experience progression; however, CF management has improved over time in concert with scientific and medical discoveries\(^1,^{7}\)

BROUGHT TO YOU BY VERTEX, because we believe that knowledge empowers you and your patients. More resources are available for you at CFSourceHCP.com, and for your patients at CFSource.com.
Reference:

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