Cystic Fibrosis: Early intervention strategies

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Early interventions in CF

Objectives

• Understand the importance of early intervention in CF lung disease
• Appreciate the different techniques for early diagnosis of pulmonary abnormalities in CF patients
• Critically appraise the different treatment options for early intervention in CF

CF: a paediatric disease?

56% of individuals in Canada were over 18 years of age in 2007

Nutrition and survival

The Toronto Experience

<table>
<thead>
<tr>
<th>Boston</th>
<th>Toronto</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>499</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>0-45 yrs</td>
</tr>
<tr>
<td>nutrition</td>
<td>low fat</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>33</td>
</tr>
<tr>
<td>Median survival</td>
<td>21 yrs</td>
</tr>
</tbody>
</table>

Corey M, J Clin Epidemiol 1988

Mucociliary clearance
**Mucociliary clearance**

The importance of ASL hydration

NEJM 2006

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**ASL depletion in CF**

Cystic Fibrosis mucociliary transport

Depletion of airway surface fluid

NEJM 2006

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**CF Pathophysiology**

CFTR gene defect
Defective ion transport
Airway surface liquid depletion
Defective mucociliary clearance
Mucus obstruction
Infection
Inflammation

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**Outcome measures in CF**

which parameter to use?

Growth
Microbiology
Inflammatory Markers
Lung Function
Pulmonary Exacerbation Rate
Quality of Life
CXR
HRCT
Newer Imaging

Rosenfeld M, PATS 2007

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**Cystic Fibrosis**

Risk factors for lung function decline

<table>
<thead>
<tr>
<th>Factor</th>
<th>Ages 6-8</th>
<th>Ages 9-12</th>
<th>Ages 13-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% predicted)</td>
<td>P-value</td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Baseline FEV1</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>.984</td>
<td>.984</td>
<td>.984</td>
</tr>
<tr>
<td>Weight-for-age percentile</td>
<td>.242</td>
<td>.292</td>
<td>.211</td>
</tr>
<tr>
<td>Sputum</td>
<td>.111</td>
<td>.003</td>
<td>.003</td>
</tr>
<tr>
<td>Crackles</td>
<td>.004</td>
<td>.032</td>
<td>.010</td>
</tr>
<tr>
<td>Wheezing</td>
<td>.524</td>
<td>.009</td>
<td>.066</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>.050</td>
<td>.306</td>
<td>.451</td>
</tr>
<tr>
<td>IV exacerbations</td>
<td>.006</td>
<td>.159</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Elevated LFT</td>
<td>.984</td>
<td>.034</td>
<td>.417</td>
</tr>
<tr>
<td>Pancreatic enzyme use</td>
<td>.023</td>
<td>.721</td>
<td>.041</td>
</tr>
</tbody>
</table>

*Relative to no decline

Konstan MW et al, J Pediatr 2007

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**Median FEV1 (% predicted) in Canada**

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Median FEV1 (% predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>90</td>
</tr>
<tr>
<td>2007</td>
<td>80</td>
</tr>
</tbody>
</table>
Unevenness of Ventilation in CF
Mucus Retention
Inflammation
Airway Wall Structural Damage

CT abnormalities in CF infants

Multiple breath washout

Lung clearance index in CF

Sensitivity to detect lung disease

<table>
<thead>
<tr>
<th></th>
<th>Bronchiectasis</th>
<th>HRCT score</th>
<th>Air trapping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>85%</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>Specificity</td>
<td>50%</td>
<td>65%</td>
<td>43%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>19%</td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td>Specificity</td>
<td>89%</td>
<td>100%</td>
<td>89%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>62%</td>
<td>63%</td>
<td>75%</td>
</tr>
<tr>
<td>Specificity</td>
<td>83%</td>
<td>88%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Is LCI responsive to treatment?

*HS/dornase alfa studies*

Hypertonic saline study

Dornase alfa study

Key inclusion criteria

FEV₁ > 80%
Age 4-18 years
Clinical stability

NCT00635141 & NCT00557089
**LCI in interventional studies**

- Hypertonic saline

<table>
<thead>
<tr>
<th></th>
<th>LCI in Saline</th>
<th>LCI in Hypertonic Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Post Hoc Sample Size Calculation**

<table>
<thead>
<tr>
<th>Outcome Analysis</th>
<th>Treatment Effect*</th>
<th>Required Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>1.78 ± 11.95</td>
<td>356</td>
</tr>
<tr>
<td>FEF 25-75 %</td>
<td>5.26 ± 22.26</td>
<td>143</td>
</tr>
<tr>
<td>CFQ-R Domains</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>2.87 ± 14.22</td>
<td>195</td>
</tr>
<tr>
<td>CFQ-R Parent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domains</td>
<td>5.91 ± 16.15</td>
<td>61</td>
</tr>
</tbody>
</table>

**CF early intervention**

- Infant pulmonary function testing

**Lung function in newborn screened CF patients**

<table>
<thead>
<tr>
<th>Age</th>
<th>FVC1.5 L (cc)</th>
<th>FVC4 L (cc)</th>
<th>FEF25-75 % (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Early intervention in CF**

- Therapeutic options
  - Promote ion transport
  - Improve clearance of airway secretions
  - Treatment of infection
  - Treatment of inflammation

**CFTR Mutation Specific Treatment**

- Class I: Defective synthesis
- Class II: Defective processing
- Class III: Defective regulation
- Class IV: Defective conductance
- Class V: Reduced quantity
**Improving Protein Expression**

*Ignore the Nonsense*

- Ribosome
- Productive translation
- Stop codon
- mRNA
- Truncated protein

Schmitz A & Famulok M. Nature 2007

**PTC124**

*Effect on Chloride Transport*

- mRNA (n=23)
  - Δ=7.1 mV
  - p<0.0001

- mRNA (n=21)
  - Δ=3.7 mV
  - p=0.032

Koren et al., Lancet 2008

**Correctors & Potentiators**

*Designed to Restore Defective CFTR Function*

- Correctors increase CFTR trafficking
- Potentiators increase CFTR gating

Ramsey et al., NEJM 2011

**CFTR potentiator ivacaftor**

*Clinical effects*

Koren et al., Lancet 2008

**CFTR potentiator ivacaftor**

*Effects on sweat chloride*

Ramsey et al., NEJM 2011

**Improving Ion Transport**

*It’s Not Just CFTR*

- Sodium channel blocker
- ENaC
- CFTR
- Gene therapy
- CFTR pharmacotherapy

*Calcium activated chloride channel*
Early intervention in CF

therapeutic options

• promote chloride transport

• improve clearance of airway secretions

• treatment of infection

• treatment of inflammation

Dornase alfa in patients with mild disease

FEV₁

Dornase alfa in patients with mild disease

FEF 25-75

Dornase alfa in CF

effect on lung function decline

Hydration therapy

The surfer’s story

Osmotic Treatment in CF

Quan et al., J Peds, 2001

Quan et al., J Peds, 2001

Konstan M et al., Peds Pulmonol 2011

Ratjen F NEJM 2006
When to initiate therapy in CF patients?

**CF doctor**

**CF patient**

Tolerability of HS in CF infants

Subbarao et al., Pediatr Pulmonol 2007

Inhaled Saline Infant Study (ISIS)

- Randomized trial planning to recruit 300 CF infants
  - 12 months double blind controlled trial
  - 7% versus 0.9% saline
- Main outcome parameters
  - Pulmonary exacerbations requiring antibiotic treatment
  - Infant pulmonary function (FRC, RV/TLC, expiratory flows)

| Arm 1 | Isotonic saline |
| Arm 2 | Hypertonic saline |
| month 0 2 4 6 8 10 12 |  |

ISIS Recruitment

344 subjects screened, 328 received test dose, 321 randomized

Bronchitol (inhaled Mannitol)

- Osmotically active sugar
- Mannitol dry powder
- 400mg = 10 x 40mg caps (bd)
- Respirable particles - 3µm

Lung function effects of mannitol

Change in FEV₁ (absolute by mL, and relative by %)

<table>
<thead>
<tr>
<th>Study</th>
<th>Change from Baseline (mL)</th>
<th>% Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPM-CF-201</td>
<td>121</td>
<td>7.0</td>
</tr>
<tr>
<td>DPM-CF-202</td>
<td>150</td>
<td>8.8</td>
</tr>
<tr>
<td>DPM-CF-203</td>
<td>83</td>
<td>6.4</td>
</tr>
<tr>
<td>DPM-CF-301</td>
<td>118</td>
<td>6.2</td>
</tr>
<tr>
<td>DPM-CF-302</td>
<td>107</td>
<td>8.2</td>
</tr>
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</table>
Early intervention in CF
therapeutic options
• promote chloride transport
• improve clearance of airway secretions
• treatment of infection
• treatment of inflammation

Early diagnosis of infection in CF
What are the consequences?
• Treatment of early *P. aeruginosa*
infection reduces the risk of chronic infection and eradicates the organism in the majority of patients

Littlewood J, Lancet 1985
Valerius et al., Lancet 1991
Frederiksen et al., Pediatr Pulmonol 1997
Wiesemann et al., Pediatr Pulmonol 1998
Ratjen et al., Lancet 2001
Gibson et al., AJRCCM 2003

ELITE* Study
*Early Inhaled Tobramycin for Eradication*
• Randomized, open-label (21 European sites)
  – 28 days vs. 56 days 300 mg inhaled tobramycin (TIS) bid
• Outcome parameters
  – Time to next positive *P. aeruginosa* culture
  – Rate of *P. aeruginosa* + cultures 28 days off study drug

ELITE: efficacy
Efficacy in sputum and non-
sputum producing patients
**EPIC Study design**
*(at first *Pseudomonas* detection)*

- TIS + *cipro*
- TIS + placebo

<table>
<thead>
<tr>
<th>Month</th>
<th>Visit</th>
<th>Solid blocks – chronic intermittent treatment</th>
<th>Striped blocks – treatment only when culture positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EPIC Study: Results**

- Cycled Therapy
- Culture-based Therapy
- TIS and *cipro*
- TIS and Placebo

**Early intervention in CF**

*therapeutic options*

- promote chloride transport
- improve clearance of airway secretions
- treatment of infection
- treatment of inflammation

**CF early intervention**

*Anti-inflammatory therapy*

- What is the right balance between infection and inflammation?

**CF Antibiotic Therapy**

*Azithromycin*

- Established therapy for patients with *P. aeruginosa* infection
- Mechanism of action still unclear (antibiotic versus anti-inflammatory)
- Anti-inflammatory effect suggested by in vitro studies and by efficacy in non infected patients (Bronchiolitis obliterans)

**Azithromycin in mild disease**

- Randomized trial in 250 CF patients without *P. aeruginosa* infection
  - 6 months double blind placebo controlled trial
  - 6 months open label treatment
- Main outcome parameters
  - Differences in absolute lung function (FEV₁)
  - Rate of pulmonary exacerbations

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Azithromycin</td>
<td></td>
</tr>
</tbody>
</table>

PI team: Lisa Saiman, Mike Anstead, Felix Ratjen, Larry Lands
**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin (N=131)</th>
<th>Placebo (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>10.7</td>
<td>10.6</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>54 (41%)</td>
<td>59 (46%)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔF508/ΔF508</td>
<td>57 (44%)</td>
<td>61 (47%)</td>
</tr>
<tr>
<td>ΔF508/other</td>
<td>40 (31%)</td>
<td>41 (32%)</td>
</tr>
<tr>
<td>Other (non ΔF508)</td>
<td>15 (12%)</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>FEV1 % Predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>50%-80%</td>
<td>18 (14%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>&gt;80%-110%</td>
<td>84 (64%)</td>
<td>93 (72%)</td>
</tr>
<tr>
<td>&gt;110%</td>
<td>28 (21%)</td>
<td>28 (22%)</td>
</tr>
<tr>
<td>Mean FEV1 (% predicted)</td>
<td>97.7</td>
<td>99.6</td>
</tr>
<tr>
<td>Mean Weight (kg)</td>
<td>37.4</td>
<td>37.7</td>
</tr>
<tr>
<td>Mean Height (cm)</td>
<td>142.6</td>
<td>141.4</td>
</tr>
</tbody>
</table>

**Proportion of Subjects Exacerbation Free**

- Azithromycin
- Placebo

Saiman et al., *JAMA* 2010

**Early intervention**

*Summary*

- Further improvements in patients’ outcomes require early intervention in children with minimal symptoms.
- Treatment strategy move from addressing the downstream effects of CFTR dysfunction to targeting the basic defect (BREATHE program, CFTR pharmacotherapy, Ion transport modulators).
- This requires more sensitive techniques to detect and monitor lung disease.

**Change in BMI (kg/m²)**

\[ p < 0.001 \]

Saiman et al., *JAMA* 2010

**Acknowledgements**

A special thank you to our patients & families!