Lung Transplantation in Cystic Fibrosis Patients


PULMONARY INSTITUTE, RABIN MEDICAL CENTER (BELINSON CAMPUS), PETACH TIQVA, ISRAEL

CF ISRAELI CONFERENCE 2015
‘Beginning of new era’ in the treatment of cystic fibrosis

- Cystic fibrosis is a life-threatening disease, but we are living in a new era with huge progress in treatment options.
- As a result, life expectancy is increasing...
Lung Transplantation:

- However... as CF treatments and survival evolve, lung transplantation is still the last therapeutic option for end-stage lung disease.
History of Lung Transplantation

- **1963**: 1st human lung transplantation (Hardy)
- **1981**: heart-lung (Shumway, Stanford)
- **1983**: single lung (Cooper, Toronto)
- **1986**: double lung (Cooper, Toronto)
- **1988**: 1st heart-lung transplantation for CF (Wallwork, Cambridge)

Successful lung transplantations opened an opportunity for more than 2500 CF patients being transplanted worldwide per year.
Adult lung transplantation according to indication and year of transplantation (transplants: 1990 to 2012).

CF constitutes the third main indication for lung transplantation, after COPD and ILD.
Local history in Israel

• 1992: First single lung transplantation in Israel
• 1996: First lung transplantation in CF in Israel
• TODAY: Rabin Medical Center - the national center for lung transplantation and follow-up in Israel With 568 lung transplants

Aravot D, Kramer M, et al.  
The Israeli experience and the characteristics for success

1996-2014

We aimed to evaluate the Israeli national experience with lung transplantation for patients with CF at Rabin Medical Center (RMC), and to assess the characteristics of CF patients that correlate with better outcomes.
Lung transplantation in CF patients – Study Methods:

Data collection
- CF patients
- Transplantation files
- 1996-2014

Description
- Numbers
- Percentiles

Analyses
- Impact of variables on:
  - Survival
  - BO

We retrospectively reviewed the medical charts of all CF patients who underwent lung transplantation between January 1996 and December 2014 at Rabin Medical Center.
Referral indications for transplantation:

- As a rule, all recipients were selected according to the International Society for Heart and Lung Transplantation (ISHLT) guidelines:
  - FEV$_1$ % < 30% or a rapid lung function decline (particularly in a female patient)
  - 6-minute walk distance of <400 m
  - Pulmonary hypertension
  - Clinical decline with:
    - Acute respiratory failure requiring non-invasive ventilation
    - Increasing antibiotic resistance
    - Poor recovery from exacerbations
    - Worsening nutritional status
    - Pneumothorax
    - Life-threatening hemoptysis despite bronchial embolization

When the life expectancy for the next 2 years is less than 50%
## Results: Demographics

### Total:
- Patients - 50
- Transplantations - 54
  - Second transplantation - 3
  - Third transplantation - 1

### Age: Mean age:
- 28.3 ± 9.1 years (range 11-50)

### Gender:
- Males - 24 (48%)
- Females - 26 (52%)

### Ethnicity:
- Jews - 42 (84%)
- Arabs - 8 (16%)
## Respiratory Characteristics...

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>O₂ dependence</strong></td>
<td>45 (90%)</td>
</tr>
<tr>
<td><strong>Bipap</strong></td>
<td>34 (68%)</td>
</tr>
<tr>
<td><strong>Tracheostomy</strong></td>
<td>2 (4%)</td>
</tr>
<tr>
<td><strong>Mechanical (Invasive) ventilation</strong></td>
<td>3 (6%)</td>
</tr>
<tr>
<td><strong>Novalung</strong> <em>(Artificial Lung Device)</em></td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Mean O₂SAT</strong></td>
<td>89.2% ± 3.9</td>
</tr>
<tr>
<td><strong>Mean PCO₂</strong></td>
<td>57.3 ± 9.7 mmHg</td>
</tr>
</tbody>
</table>

* Novalung = Artificial Lung Device, a bridge to transplantation
### CF patients characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic insufficiency</td>
<td>46</td>
<td>(92%)</td>
</tr>
<tr>
<td>CF Related Diabetes</td>
<td>36</td>
<td>(72%)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>8</td>
<td>(16%)</td>
</tr>
<tr>
<td>Gastrostomy</td>
<td>18</td>
<td>(36%)</td>
</tr>
</tbody>
</table>

- **Mean HBA1C**: $7.17 \pm 2.7\%$
- **Liver disease**: 8 (16%)
- **Gastrostomy**: 18 (36%)
- **Mean BMI**: $17.8 \pm 3.4$ kg/m$^2$
- **Mean Weight**: $48.7 \pm 9.6$ kg
- **Mean Height**: $162.6 \pm 10.4$ cm
Type of transplantation

- 89% 2 lungs
- 7% heart and 2 lungs
- 4% 1 lung * d/t previous pneumonectomy

N=54 transplantations
Operative & Perioperative data:

Ischemia time graph

Mean Ischemia time 259 ± 67 min (~4 hours) for the 2’nd lung

Cold Ischemia Times

<table>
<thead>
<tr>
<th>Organ</th>
<th>Accepted CIT Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>3-4</td>
</tr>
<tr>
<td>Lung</td>
<td>3-5</td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;24</td>
</tr>
<tr>
<td>Kidney (CS)</td>
<td>24-36</td>
</tr>
<tr>
<td>Kidney (MP)</td>
<td>72</td>
</tr>
<tr>
<td>Pancreas</td>
<td>12-24</td>
</tr>
<tr>
<td>Intestine</td>
<td>6</td>
</tr>
</tbody>
</table>
Operative & Perioperative data:

- ECMO during operation: 17 (31%)
- Mean ICU LOS: $12 \pm 22$ days
- Mean Department LOS: $16.3 \pm 23$ days

ECMO = Extracorporeal Membrane Oxygenation
ICU = Intensive Care Unit
LOS = Length of stay
Transplantation results...
Pulmonary function improved from FEV$_1$% predicted of 23.6±6% preoperatively to 72.45±19.4%, 1 year post transplantation. There is a parallel increase in FEV1 and BMI till they get to a plateau after 1 year.
Survival:

For the whole group actuarial survival rates are:

- 83% for 1 year
- 68% for 3 years
- 62% for 5 years
- and 39% for 10 years
Variables correlated with better survival:

I. No Liver Disease

II. Less Ischemia time

$p$ value = 0.012

Survival rates

No liver disease

Liver disease

$p$ value = 0.023

Survival rates

<300 min

> 300 min
III. BMI correlated with better survival:

In a multi-variant analysis, using Cox regression, we found that BMI 1 year post transplantation is the sole determinant and the most influencing variable on survival.
IV. FEV1% 6 months post trans. correlated with survival:

1 Blue line = FEV1% ≤20  
2 Green Line = 20 < FEV1% ≤30  
3 Brown line = FEV1% > 30

p value = NS 0.5

1 Blue line = FEV1% ≤40  
2 Green Line = 40 < FEV1% ≤60  
3 Brown line = FEV1% > 60  

p value < 0.001
No correlation with better/worse survival

Pancreatic sufficiency

CF Related Diabetes

PEG usage

P value = NS \( m/p \) d/t small numbers of PS

P value = NS 0.2 \( m/p \) d/t small numbers of non CFRD

P value = NS 0.48

Also: Gender, age, type of transplantation, oxygen dependency, BIPAP usage, \( O_2 \) saturation, ECMO during surgery, stent insertion.
Perioperative complications: Always better without

\[ p \text{ value} = 0.008 \]
Complications: Early/Peri-Operative

• Total N=47
  • No complications (45%)
  • Yes complication (55%)

• Type
  • Acute infections* 12 (25%)
  • Pnemothorax/Pleural Effusion 9 (19%)
  • Vascular hemostasis** 7 (15%)
  • Pulmonary edema 6 (12%)
  • Neurology*** 6 (12%)
  • Hyperacute/Acute rejection/ Graft malfunction 4 (8%)
  • MOF/ Renal/ Liver failure 4 (8%)
  • Early death 6 (12%)

At 30 days following operation

*Sepsis; Pneumonia; Line infection

**Bleeding; Thrombosis; Vascular stenosis

***Stroke; Ptosis; Vocal cord paralysis
Late complications

<table>
<thead>
<tr>
<th>Late complications</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total complications N=118</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anastomosis complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIOS (Distal Intestinal Obstruction Syndrome)</td>
<td>7</td>
<td>5.9%</td>
</tr>
<tr>
<td>Gastroparesis, GERD, Aspirations</td>
<td>8</td>
<td>6.7%</td>
</tr>
<tr>
<td><strong>Diaphragmatic paresis</strong></td>
<td>11</td>
<td>9.3%</td>
</tr>
<tr>
<td><strong>Sinusitis</strong></td>
<td>10</td>
<td>8.4%</td>
</tr>
<tr>
<td>Neurology complications</td>
<td>9</td>
<td>7.6%</td>
</tr>
<tr>
<td><strong>Lung Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia/Necrotizing pneumonia</td>
<td>8</td>
<td>6.7%</td>
</tr>
<tr>
<td><strong>Nephrology complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure/Nephrolithiasis</td>
<td>8</td>
<td>6.7%</td>
</tr>
<tr>
<td><strong>PTLD (Post Transp. Lymphoproliferative disease)</strong></td>
<td>5</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

Also: Pleural/pericardial Effusion/Pneumothorax, Hematologic comp., Sepsis, Skin Infection/Rash, Thrombosis/edema, Cholestasis/Cholecystitis/Liver enzyme elevation/Pancreatitis, Subglotic stenosis, DKA, Cataract, Arthritis/Arthralgia, MI/CHF.
## Management of Complications

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastomosis treatment</td>
<td>32</td>
<td>(63%)</td>
</tr>
<tr>
<td>FESS</td>
<td>6</td>
<td>(12%)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>3</td>
<td>(6%)</td>
</tr>
<tr>
<td>Gastrointestinal procedures</td>
<td>3</td>
<td>(6%)</td>
</tr>
<tr>
<td>(Cholecystectomy, Colonoscopy, Balloon dilatation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>2</td>
<td>(4%)</td>
</tr>
<tr>
<td>Pericardiotomy</td>
<td>1</td>
<td>(2%)</td>
</tr>
<tr>
<td><strong>Total treatments</strong></td>
<td><strong>N=51</strong></td>
<td></td>
</tr>
</tbody>
</table>

**FESS** = Functional Endoscopic Sinus Surgery
## Treatments for anastomotic stenosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser bronchoscopy</td>
<td>9</td>
<td>28%</td>
</tr>
<tr>
<td>Balloon dilatation</td>
<td>7</td>
<td>21%</td>
</tr>
<tr>
<td>Stent insertion</td>
<td>6 patients</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>8 stents</td>
<td></td>
</tr>
<tr>
<td>Granulation/Polyp removal</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td>Mechanical dilatation</td>
<td>3</td>
<td>9%</td>
</tr>
<tr>
<td>Amplatzer device</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Brachitherapy</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Total treatments</strong></td>
<td><strong>N = 32</strong></td>
<td></td>
</tr>
</tbody>
</table>
**Lung infections:** The bug will not disappear...

### Pre - transplantation:
- **Pseudomonas** 50 (100%)
- Aspergillus 22 (44%)
- Acinetobacter 1 (2%)
- MSSA 10 (20%) MRSA 2 (4%)
- Stenotrophomonas 5 (10%)
- Serratia 2 (4%)
- Achromobacter 0 (0%)
- Klebsiella 1 (2%)
- NTM 7 (14%)
- Nocardia 2 (4%)
- ABPA 3 (6%)
- Burkholderia cepacia 0 (0%)

### Post - transplantation:
- **Pseudomonas** 50 (100%)
- Aspergillus 24 (48%)
- Acinetobacter 11 (22%)
- MSSA 14 (28%) MRSA 2 (4%)
- Stenotrophomonas 6 (12%)
- Serratia 5 (10%)
- Achromobacter 2 (4%)
- Klebsiella 3 (6%) CRE 1 (2%)
- NTM 3 (6%)
- Nocardia 1 (2%)
- ABPA 1 (2%)
- Burkholderia cepacia 0 (0%)
What about chronic transplant associated lung disease?

Chronic lung rejection is still the most important late complication... results in BOS or RLD
Bronchiolitis Obliterans Syndrome

• What are the variables that are related to early or late BOS?

• Definition:
  • BO1 When FEV1 decrease in 20% or more from the maximum FEV1 after transplantation
Earlier BOS correlated with:

I. Gender

Males had more time of freedom from BOS

p value = 0.039
Earlier BOS correlated with: II. Arab > Jewish Ethnicity

p value = 0.007
Earlier BOS correlated with: III. Younger Age

- $1 = \text{age} \leq 20$
- $2 = 20 < \text{age} \leq 30$
- $3 = 30 < \text{age} \leq 40$
- $4 = 40 < \text{age} \leq 50$
- $5 = \text{age} > 50$

p value < 0.001
Earlier BOS correlated with: IV. **BMI**

**pre-transplantation**
- BMI < 18
- BMI > 25

**6 month post trans.**
- BMI < 18
- BMI > 25

**1 year post trans.**
- BMI < 18

- **p value < 0.001**
- **p value = 0.083 trend but NS**
- **p value = 0.028**
BOS was not correlated with:

- Pancreatic sufficiency
- CF Related Diabetes
- Liver disease

Also: Type of transplantation, oxygen dependency, BIPAP usage, $O_2$ saturation, gastrostomy, ECMO during surgery, stent insertion.
Discussion & Summary:

• Lung transplantation confers a survival advantage

• RMC actuarial survival rates are similar to ISHLT 2014 rates


• Also similar to a large study at UK on lung transplantation among CF patients, with a 1 year survival rate of 82% and 5 year survival of 62%

Nutritional status after transplantation seems to be more important than the nutritional status before the transplantation.

Is it the weight gain that improved survival or is it the better transplantation course that improved the weight?

Pancreatic sufficiency or insufficiency not associated with worse or better survival post-transplant.

This was opposite to the Canadian study who found pancreatic sufficiency to worsen survival [Stephenson AL et al. J Heart Lung Transplant. May 2015]
Discussion & Summary: “Gender Gap”

• In our study, gender was not significantly correlated with survival
  • Similar to other studies on CF transplantations
  • Different from studies on all other reasons for transplantation, in which females are usually the “Strong gender” [J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095]

• But...there is a significant correlation between gender and BOS
  • In our study males had more freedom from BOS and a better course of post-transplant disease.
  • This “gender gap”, in which females with CF appear to have higher morbidity and mortality than males, is hypothesized to be due to the pro-inflammatory effects of estrogens. [AU Sweezy NB et al. The cystic fibrosis gender gap: potential roles of estrogen. Pediatr Pulmonol. Apr 2014]
Discussion & Summary: Ethnicity

- Arab ethnicity was correlated with more BOS and shorter freedom from BOS.
- We don't know the reasons for these outcomes in the Arab population.
- Assuming no difference in adherence to treatment and follow-up...
- More passive smoking?
  

- Allen et al. presented that race matching resulted in an improvement in long-term survival. Maybe differences in donor ethnicity correlated with less freedom from BOS?
  

- Further study is necessary to investigate the impact of post-transplant management on survival in this population.
Happy Results!
THANKS!