Health Related Quality of Life in Lung Transplantation: What is it and Why Does it Matter?

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Talk Overview

• Evolution of the Clinical Aims of LTx
• Define Health Related Quality of Life (HRQL)
• Review the Existing Literature in LTx
Goals of this Talk

- Highlight the primacy of HRQL assessing LTx efficacy
- To understand how HRQL is defined in academic literature
- By reviewing existing literature
  - Provide estimates of the magnitude & durability of improvement
    - Improve pre-transplant counseling
    - Identify times post-tx at high risk for poor outcomes
  - Identify determinants of HRQL
    - Develop interventions
A bit of history…
A bit of history…

- **1963**: James Hardy performs first LTx
  - Patient: Jail inmate; PMH: lung CA, kidney insufficiency
  - Survived 18 days

- **1963-83**: 40 more attempts at LTx
  - Most survived < 2wks (high doses of prednisone)

- **1983**: FDA approves **Cyclosporin** for renal tx
  - Joel Cooper performs LTx on a 58yo w/ Idiopathic Pulmonary Fibrosis (lower doses of prednisone)
  - Survives 8 years; dies of renal failure
The Cyclosporine Revolution

Number of transplants

- Total
- Bilateral/Double Lung
- Single Lung

Data from 1985 to 2009, showing an increase in the number of transplants over the years.
Evolving Clinical Aims of LTx

- The *original* aim: Do one.
- A new aim identified: Extend survival after LTx
Evolving Clinical Aims of LTx

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Evolving Clinical Aims of LTx

- The *original* aim: Do one.
- A new aim identified: Extend survival after LTx
- Today, Aims of LTx are to:
  - Extend Survival *and*
  - Improve HRQL

Scleroderma-interstitial lung disease 2 years after LTx
Research and Policy Outcomes Remain Antiquated:

Success = Not Dead
“Net-benefit” of LTx:

Survival time
Defining Success in Research ≠ Clinical Goals

- Improve Survival

and

- Palliate symptoms
- Return to meaningful activities
- Increase functioning
- Improve HRQL

Cystic Fibrosis 6yrs after LTx
Success is More Than Survival…but How Do you Measure That?

5 yrs post-LTx for Osler-Weber-Rendu pulmonary hypertension

1 yr post-LTx for Scleroderma ILD

6 yrs post-LTx for Cystic Fibrosis
Health-Related Quality of Life

SF-36 Score = 48
SF-36 Score = 43
SF-36 Score = 38
Initial Reactions
WHY?
HRQL is Multidimensional

Self-perceived effects of health, and illness (and consequent medical therapy) on QOL
HRQL is Multidimensional

Effects of health, and illness (and consequent medical therapy) on QOL

HRQL

- Physical functioning
- Energy/Fatigue
- Adaptation to Disease
- Emotional status
- Cognitive Performance
- Symptoms
Measuring HRQL

- **Generic Measures**
  - Broadly applicable
  - Compares across diseases
  - Captures systemic side effects of tx
  - May be less sensitive to change
  - May not measure what is important

- **Disease Specific Measures**
  - QOL impacted by specific disease and tx
  - More responsive and discriminative within disease
  - Can’t compare different diseases
  - Less responsive to systemic effects of disease or treatment
Different Ways of Scoring HRQL

• **Single “Index” Score**
  
  – Better is better: 43 > 32 (for SF-36)
  
  – Decision-making is simplified
  
  – Commonly used in clinical trials
  
  – Informs policy decision-making
Different Ways of Scoring HRQL

- **Domain Specific**
  - Scoring reflects multidimensional nature of HRQL.
  - Identifies targets for intervention
What do we know about HRQL in adult LTx today?

- 61 published studies 1/1/2000-12/31/2011
  - 73 since 1983
- 61 studies can be categorized into 6 themes
  1. Comparisons of HRQL before and after LTx
  2. Longitudinal Studies of HRQL after LTx
  3. Determinants of HRQL
  4. Psychosocial Factors affecting HRQL
  5. Therapies and Interventions aimed at Improving HRQL
  6. Instrument Validation and Methodology
1. Pre- and Post-LTx comparisons

- 25 studies
- HRQL improved in nearly all studies
  - Domains affected: physical health and functioning
  - Improvement was substantial and significant
- Changes in emotional well-being & mental health domains were small or not significant
- Most studies identified residual impairments in HRQL
- Those with the worst HRQL before LTx have the greatest improvement post-LTx\(^1\)

\(^1\)Singer, et al. CHEST 2011; 140:1023A
• 12 studies
• HRQL improves substantially in the 1st year
  – Greatest gain is within the 1st 6 months
• HRQL trajectory after 1 year is heterogeneous
  – Declines associated with bronchiolitis obliterans syndrome and comorbid illnesses
  – Impairment after LTx never reaches pre-LTx levels
3. Determinants of HRQL

- 25 studies
- BOS most commonly studied
  - BOS is associated with poorer HRQL
    - Consistent across all HRQL instruments including generic, disease-specific, and utility instruments
  - Impacts domains relating to functioning, energy, and mobility
  - But, studies predominantly cross-sectional
    - 2 studies (51 pts total) compared HRQL before and after BOS developed in the same subjects
3. Determinants of HRQL

- Transplant type (6 studies) = equivocal
- Bilateral and Heart-Lung *may* have better HRQL than Single LTx
  - Single LTx had ↑ pain and ↓ HRQL than Bilateral LTx in one study; another study found the opposite (SF-36)
- Cystic fibrosis *may* be associated with better HRQL compared to other diagnoses
- LTx ➔ greatest improvement in HRQL compared to liver or kidney
3. Determinants of HRQL

- Other factors that may impact HRQL:
  - Side effects of immunosuppression
  - Pain
  - Poor energy
  - Acute rejection
  - Infections
  - Olfactory performance
  - Exercise tolerance and mobility
4. Psychological Factors

- 15 studies
- Most focused on depression and anxiety symptoms
- Other factors studied (n=1 each)
  - PTSD, burden on relationships, adjustment to illness, feelings of responsibility to donors and caregivers, low self esteem, decreased sexual drive
Psychological Factors Drive HRQL in the 1st year post-LTx

- 112 subjects surveyed at 2, 7, 12m post-LTx
- Outcome: HRQL assessed by SF-36
- Predictors:
  - Optimism (Life Orientation Test)
  - Mastery (Sense of Mastery Scale)
  - Caregiver support (Investigator designed support model)
  - Friend support (12-item measure)
  - Religiosity (3-item measure adapted from King & Hunt)
  - Coping strategies (Brief COPE scale)

Myaskofsky L. Am J Transplant. 2006
Psychological Factors Drive HRQL

- Optimism predicted general health, vitality, social functioning, and mental health.
- Support from friends predicted vitality and mental health.
- Avoidant coping predicted physical functioning.
5. Therapies and Interventions

- 10 studies
  - 6 involved behavioral interventions
- Data is heterogeneous and limitations preclude conclusions in all but 1 study
5. Exercise Training in LTx

- RCT of 3m of supervised exercise training
  - Randomized adults age 40-65 at discharge after LTx
- Outcomes:
  - 1°: Daily walking time
  - 2°: HRQL (SF-36), mood (HAD), time spent in different postures, daily steps, movement intensity, time spent in moderate intense activities, exercise capacity, peripheral muscle force, pulmonary function,
- 40 randomized, 6 lost to follow-up
  - Analyzed: 18 in intervention group, 16 in control group

5. Exercise Training Improves Functioning

- At 3 months, intervention → improvements in:
  - Walking time, movement intensity, daily steps, 6MWD, quadriceps force
- At 12 months
  - Improvements maintained
  - Time spent in moderately intense physical activity
- No impact on anxiety or depressive symptoms

Exercise Training improves HRQL

<table>
<thead>
<tr>
<th>Functioning</th>
<th>Intervention (mean ± SD)</th>
<th>Control (mean ± SD)</th>
<th>Adjusted difference* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-LTx</td>
<td>19 ± 12</td>
<td>16 ± 11</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>43 ± 25</td>
<td>36 ± 24</td>
<td></td>
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</tr>
<tr>
<td>3 months</td>
<td>69 ± 16</td>
<td>60 ± 19</td>
<td>5 (-3 to 13)</td>
<td>0.213</td>
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<tr>
<td>1 year</td>
<td>77 ± 11</td>
<td>65 ± 17</td>
<td>10 (1 to 20)</td>
<td>0.039</td>
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<tr>
<th>Role Functioning</th>
<th>Intervention (mean ± SD)</th>
<th>Control (mean ± SD)</th>
<th>Adjusted difference* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-LTx</td>
<td>16 ± 28</td>
<td>9 ± 15</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>31 ± 34</td>
<td>22 ± 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>61 ± 33</td>
<td>48 ± 44</td>
<td>15 (-14 to 43)</td>
<td>0.448</td>
</tr>
<tr>
<td>1 year</td>
<td>83 ± 28</td>
<td>52 ± 32</td>
<td>29 (7 to 51)</td>
<td>0.011</td>
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Limitations in the Existing Literature

- No US study performed since the LAS was implemented
- Most were cross-sectional analyses
  - 8 studies with true longitudinal design
    - 6 studied cohorts of 22-66 pts
    - 3 studied cohorts before and after LTx
- Selection and survivorship bias
- Data scant after 1 year
  - 159 “long-term” survivors comprise LTx literature
- Incomplete or no multivariate adjustment
- A focus on single determinants in isolation
Conclusions

- LTx → Improvements in survival and HRQL for patients with end-stage lung disease
- HRQL research in LTx is nascent
  - Improvements observed in domains of physical functioning, mobility
  - Those with the worst HRQL pre-LTx derive the greatest benefit
- BOS is a determinant of poor HRQL post-LTx
Moving the field forward…

• Longitudinal, repeated measures studies of patients before and after LTx in the LAS era
  – Consideration of pulmonary and extra-pulmonary factors *simultaneously* as determinants of HRQL
  – Attention to selection and survivor bias
• More work in instrument validation
• Qualitative studies
• Consensus on instrument selection for multicenter studies
The Goals of Future Research

• More accurate estimates of the magnitude & durability of improvement
  – Improve pre-transplant counseling
  – Identify times post-tx at high risk for poor outcomes
  – *Aid in candidate selection: Who will/wont benefit?*

• Identify determinants of HRQL and their *relative* impact
  – Target *highest* impact factors for interventions
The Goals of Future Research

- Inform efforts to incorporate Patient-Centered Outcomes into organ allocation policy
  - Redefine the “net-benefit” achieved from LTx
Targeting these Goals will Help Realize the 1° Clinical Aims of LTx