A Framework for Studying Shared-Decision Making in Treatments for Food Allergy

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My disclosures haven’t changed in the last hour!
Learning Objectives

• Understand the current state of OIT
• Understand the health and economic effects related to therapy
• Understand the complexities of the choice to consider enrollment in therapy
• Understand a framework for shared decision making regarding food allergy therapy

Evolution of Food Allergy

- Initial poor awareness and recognition
- Increased awareness leads to increased diagnosis
- Diagnosis must be fine tuned, best practices established, outcomes monitored, and therapies discovered
A Delicate Balance

Treating/curing food allergy

Maximizing how we can live with food allergy

Theoretical Model

Poor understanding of disease prevalence and natural history

Poor clinical practices

Questionable definition and diagnostic criteria

Patient misunderstanding, fear, confusion and anxiety

Poor quality of life
What is Oral Immunotherapy?

- **Aim:** incrementally re-feed one’s food allergen
  - Increase tolerance to an allergen
  - Protect against accidental exposure vs. outright cure
- **Status:** experimental/investigational (NIH sponsored)
  - Unproven safety, effectiveness, mechanism of action
  - Not FDA approved, though not needed in certain instances
  - Not reimbursable through 3rd party payers
- **Issues:** no uniform method, poor study methods
  - Inconsistencies, poorly representative patients enrolled
  - Biotech, private practice competing with academic studies

How Immunotherapy Works

- **Main effect is generation of cells that facilitate tolerance**
- **Tolerance** = allergen exposure won’t result in reaction
  - Generate master cells that dampen immune response ($T_{reg}$)
- **Suppress allergic immune system (e.g. $T_{h2}$ mediators)**
  - Decrease production from IgE (allergic antibody)
  - Increase production of IgG4 (marker of tolerance vs. blocks IgE binding)
  - Suppress mediators of reactions (mast cells, basophils, eosinophils)
- **Can we distinguish tolerance vs. desensitization?**
OIT in Action

<table>
<thead>
<tr>
<th>Entry challenge</th>
<th>Rapid Desensitization</th>
<th>Maintenance</th>
<th>Interim Challenge</th>
<th>Maintenance</th>
<th>End of Maintenance challenge</th>
<th>Continuation or discontinuation</th>
<th>End of study challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-study</td>
<td>Day 1</td>
<td>Can persist for few months to 2 years</td>
<td>Variable duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Build to 12-50mg</td>
<td>Build up to ~300-800mg (varies), increase dose in office every 2 weeks</td>
<td>Placebo group cross-over</td>
<td>Continue therapy, test sustained non-response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OIT: What Do We Know

- Many can achieve some degree of desensitization
  -- Threshold increased for most but not all, effect/success poorly predicted
  -- Few have developed sustained tolerance
  -- No indication of duration of therapy or how long effect lasts
- Fairly equal effects seen with milk, egg, peanut
- Markers of allergen sensitivity diminish significantly
  -- See shift in allergen specific IgE→IgG4 and part of allergen recognized
- See variable effect of immune cell shut down
  -- No consistent biomarker pattern shown, but are many targets of interest
- There are high adverse event rates, and high pt dropout
### TABLE I. Peanut OIT studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design Description</th>
<th>Sample Size</th>
<th>Subject Age (y)</th>
<th>Maintenance dose (mg)</th>
<th>Duration</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al.</td>
<td>2009</td>
<td>Open label</td>
<td>29</td>
<td>1-16</td>
<td>1800</td>
<td>36 mo</td>
<td>93% Passed 3.5-g peanut OFC</td>
</tr>
<tr>
<td>Blumenholz et al.</td>
<td>2010</td>
<td>Randomized open label</td>
<td>23</td>
<td>3-14</td>
<td>500</td>
<td>7-d Bush escalation, 8-wk maintenance period</td>
<td>64% Reached maintenance of 500 mg of peanut</td>
</tr>
<tr>
<td>Vardanian et al.</td>
<td>2011</td>
<td>Randomized, placebo controlled</td>
<td>19</td>
<td>3-11</td>
<td>2000</td>
<td>48 wk</td>
<td>84% Passed 5000-mg peanut OFC</td>
</tr>
<tr>
<td>Anastasios et al.</td>
<td>2011</td>
<td>Open label</td>
<td>22</td>
<td>4-18</td>
<td>800</td>
<td>32 wk</td>
<td>64% Tolerated 6.6-g OFC</td>
</tr>
<tr>
<td>Anastasios et al.</td>
<td>2014</td>
<td>Randomized, controlled</td>
<td>39</td>
<td>7-16</td>
<td>800</td>
<td>26 wk</td>
<td>62% Tolerated 1400-mg challenge</td>
</tr>
<tr>
<td>Vickers et al.</td>
<td>2014</td>
<td>Open label</td>
<td>24</td>
<td>1-16</td>
<td>Up to 4000</td>
<td>Up to 5 y</td>
<td>50% SU to 5000-mg OFC after 4-wk avoidance</td>
</tr>
<tr>
<td>Nair et al.</td>
<td>2014</td>
<td>Randomized, placebo controlled</td>
<td>16</td>
<td>7-13</td>
<td>2000</td>
<td>12 mo</td>
<td>OIT &gt; SLIT in OFC threshold, low rate of SU</td>
</tr>
</tbody>
</table>

### TABLE II. Egg OIT studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design Description</th>
<th>Sample Size</th>
<th>Subject Age (y)</th>
<th>Maintenance dose (mg)</th>
<th>Duration (mo)</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchanan et al.</td>
<td>2007</td>
<td>Open label</td>
<td>7</td>
<td>1-16</td>
<td>0.3</td>
<td>24</td>
<td>57% Passed 8-g OFC</td>
</tr>
<tr>
<td>Vickers et al.</td>
<td>2010</td>
<td>Open label</td>
<td>3</td>
<td>3-13</td>
<td>0.3-3.6</td>
<td>18-30</td>
<td>75% Passed OFC 1 mo after stopping OIT</td>
</tr>
<tr>
<td>Burks et al.</td>
<td>2012</td>
<td>Randomized, placebo controlled</td>
<td>40</td>
<td>5-11</td>
<td>1.6</td>
<td>22</td>
<td>75% Passed 10-g OFC but SU in only 28% at 6-8 wk later</td>
</tr>
</tbody>
</table>
OIT: Present Knowledge

<table>
<thead>
<tr>
<th>Food</th>
<th>RCT</th>
<th>Severe pts</th>
<th>Young Children</th>
<th>Major Sx Free</th>
<th>Desensitization</th>
<th>Tolerance</th>
<th>Mechanism</th>
<th>EoE</th>
<th>Return of Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>4-6 week</td>
<td>unclear</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Milk</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None to date</td>
<td>unclear</td>
<td>Yes</td>
<td>YES</td>
</tr>
<tr>
<td>Peanut</td>
<td>Yes</td>
<td>Non-US</td>
<td>Yes (DEVIL)</td>
<td>No</td>
<td>Yes</td>
<td>Variable but limited</td>
<td>Unclear, appears tolerant</td>
<td>Yes</td>
<td>NA</td>
</tr>
</tbody>
</table>

- Better data exist in Europe—more aggressive, studied longer, but ? if translates
- Australia: exploring use of probiotics, single study, poor design
- SLIT vs. OIT still being hashed out—SLIT appears “safer” but less effective
- Limited long-term follow up exists, few studies testing sustained non-response
- EoE **most definitely** occurs, and some reactions are worse than one’s baseline
- Few studies have addressed any patient-oriented outcome
- Industry trials have started—how will these change the landscape?
- Omalizumab pre-tx, multiple food OIT still in infancy, studies poorly designed
Food Allergy QoL: Understanding the Health Benefits of Therapy

- Two types of QoL being measured
  - The patient (usually a child, directly affected by disease)
  - The parent (indirectly affected by disease, has spillover effects)
  - Unclear who is more affected or which is more important

- Are both generic, disease specific measures

- For food allergy, generic index is not sensitive
  - Low mortality, rare symptoms = no large changes in health status
  - Food allergy specific measures note the **daily burden of vigilance**
  - Often a perception that accidental ingestion will be fatal

Food Allergy Disease Burden

- Fear/persistent vigilance for accidental reaction
- Fear of hidden ingredients
- Fear of being able to treat a reaction
- Burden of no cure for the disease
- Burden of food avoidance/label reading
- Limitation on activity/travel
- Social stigma/inclusion and interactions
- Bullying
- Empowerment (or lack thereof)

QoL as an OIT Outcome Measure

- Limited patient reported outcomes from OIT
  --One US trial, one UK trial reported QoL improvement
- Stanford group investigating QoL in multi-food OIT
- Phase I patients in mOIT/Omalizumab-OIT trials
  --Noted significant improvement vs. baseline score over time (0-24 months), in all domains and at each time point
  --Noted no change in a small control group
  --Less change noted in pts with asthma or respiratory reactions during OIT, and more change in older pts or those undergoing >4 food OIT
  --Effect noted for both the mOIT and for the omalizumab trials
- Conclusions limited by validity and power issues but promising
QoL Needs Assessment

- We know patients suffer, but can we fix this?
- Understand what contributes to poor QoL
- Weight/importance of child vs. caregiver QoL
- Bark worse than the bite? Perception vs. reality
- Determine/rectify clinic vs. self-report differences
- Determine effects of MD knowledge, variation
- Does QoL differ by region of the US
- Explore relationship between QoL and self-efficacy
- Integration of QoL as a clinical and research outcome

A Quick Primer on the Costs of Food Allergy in the US

Understanding the Economic Costs that Factor into Decision Making and Potential Benefits of Therapy
**Individual and Societal Costs**

**Total Annual Cost per Child:**

$4,184

**Total Annual Cost In the U.S.:**

$24.8 billion

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**Willingness to Pay**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (in Billions)</th>
<th>Per Child</th>
<th>Total (in Billions)</th>
<th>Per Child</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WTP</strong></td>
<td>20.8</td>
<td>3504</td>
<td>(15.7-25.7)</td>
<td>(2652-4344)</td>
</tr>
<tr>
<td><strong>Costs borne by families</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-of-pocket treatment</td>
<td>5.5</td>
<td>931</td>
<td>(4.7-6.4)</td>
<td>(793-1080)</td>
</tr>
<tr>
<td>Lost labor productivity</td>
<td>0.77</td>
<td>130</td>
<td>(0.53-1.0)</td>
<td>(89-175)</td>
</tr>
<tr>
<td>Opportunity</td>
<td>14.2</td>
<td>2399</td>
<td>(10.5-18.4)</td>
<td>(1771-3104)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20.5</strong></td>
<td>3457</td>
<td><strong>(16.7-24.9)</strong></td>
<td><strong>(2816-4208)</strong></td>
</tr>
<tr>
<td><strong>Reported costs borne by families</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct medical costs</td>
<td>4.6</td>
<td>724</td>
<td>(2.8-6.3)</td>
<td>(472-1063)</td>
</tr>
<tr>
<td>Reported costs</td>
<td>24.8</td>
<td>4184</td>
<td>(20.6-29.4)</td>
<td>(3475-4960)</td>
</tr>
</tbody>
</table>
### Direct Medical Costs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Children With Visit, % (SE)</th>
<th>Visits per Child, Mean (SE)</th>
<th>Cost, US $</th>
<th>Visit</th>
<th>Child</th>
<th>Overall Annual (in Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatricist</td>
<td>42 (2)</td>
<td>.82 (.05)**</td>
<td>112</td>
<td>92</td>
<td>543</td>
<td></td>
</tr>
<tr>
<td>Allergist</td>
<td>41 (2)</td>
<td>.79 (.05)**</td>
<td>175</td>
<td>138</td>
<td>819</td>
<td></td>
</tr>
<tr>
<td>Pulmonologist</td>
<td>14 (1)</td>
<td>.07 (.01)**</td>
<td>175</td>
<td>12</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Nutritionist</td>
<td>17 (1)</td>
<td>.16 (.04)**</td>
<td>100</td>
<td>16</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Alternative Provider</td>
<td>17 (1)</td>
<td>.23 (.05)**</td>
<td>100</td>
<td>23</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>Emergency Department</td>
<td>13 (1)</td>
<td>.18 (.02)**</td>
<td>711</td>
<td>129</td>
<td>764</td>
<td></td>
</tr>
<tr>
<td>Inpatient Hospitalization Stays</td>
<td>4 (1)</td>
<td>.05 (.01)**</td>
<td>6269</td>
<td>314</td>
<td>1863</td>
<td></td>
</tr>
<tr>
<td><strong>Total Direct Medical Costs</strong></td>
<td></td>
<td></td>
<td>724</td>
<td>4292</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Direct medical costs are medical costs borne by the health care system associated with prevention, diagnosis, and treatment of food allergies.


### Out-of-Pocket Costs

<table>
<thead>
<tr>
<th>Variable</th>
<th>% Reporting Cost (SE)</th>
<th>Mean Direct Out-of-Pocket Costs, US$ (SE)</th>
<th>Cost Per Child, US$</th>
<th>Overall Annual Cost (in Millions), US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits to the physician’s office of health clinic (including copays)</td>
<td>52.5 (2.2)</td>
<td>160 (14)</td>
<td>84</td>
<td>499</td>
</tr>
<tr>
<td>Visits to the emergency room (including copays)</td>
<td>16.1 (1.6)</td>
<td>247 (42)</td>
<td>40</td>
<td>235</td>
</tr>
<tr>
<td>Overnight Stays at the hospital</td>
<td>10 (1.4)</td>
<td>411 (182)</td>
<td>41</td>
<td>244</td>
</tr>
<tr>
<td>Travel to and from health care visits (including ambulance use; parking expenses)</td>
<td>27.7 (1.8)</td>
<td>91 (14)</td>
<td>25</td>
<td>149</td>
</tr>
<tr>
<td>Epinephrine injectors</td>
<td>35.9 (1.9)</td>
<td>87 (4)</td>
<td>31</td>
<td>184</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>50.8 (2.2)</td>
<td>62 (4)</td>
<td>32</td>
<td>188</td>
</tr>
<tr>
<td>Other prescription/nonprescription medications</td>
<td>29.3 (1.9)</td>
<td>122 (13)</td>
<td>36</td>
<td>211</td>
</tr>
</tbody>
</table>

### Opportunity Costs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reporting, % (SE)</th>
<th>Opportunity, Mean (SE)</th>
<th>Per Child</th>
<th>Overall Annual (in Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Career has been restricted</td>
<td>5.7 (0.9)</td>
<td>15 655 (2471)</td>
<td>892</td>
<td>5.3</td>
</tr>
<tr>
<td>A job had to be given up</td>
<td>4.9 (0.7)</td>
<td>29 657 (4151)</td>
<td>1453</td>
<td>8.6</td>
</tr>
<tr>
<td>A job was lost through dismissal</td>
<td>1.9 (0.6)</td>
<td>14 849 (7479)</td>
<td>282</td>
<td>1.7</td>
</tr>
<tr>
<td>A job change was required</td>
<td>2.5 (0.6)</td>
<td>10 605 (3161)</td>
<td>265</td>
<td>1.6</td>
</tr>
<tr>
<td>Any job-related opportunity cost (total amount)**</td>
<td>9.1 (1.0)</td>
<td>32 719 (4166)</td>
<td>2977</td>
<td>17.6</td>
</tr>
<tr>
<td>Any job-related opportunity cost (maximum amount)***</td>
<td>9.1 (1.0)</td>
<td>26 363 (2545)</td>
<td>2399</td>
<td>14.2</td>
</tr>
</tbody>
</table>

*Opportunity cost is the additional cost associated with activities forgone as a result of a child’s food allergy
**All possible responses were used to calculate job-related opportunity cost
***Only the maximum of 4 possible responses was used to calculate job-related opportunity cost

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### Income Disparity of Costs

<table>
<thead>
<tr>
<th>Type of Cost</th>
<th>&lt;$50K</th>
<th>$50K-99K</th>
<th>≥$100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Direct Costs borne by health care system</td>
<td>1374 (274)</td>
<td>1024 (125)</td>
<td>940 (128)</td>
</tr>
<tr>
<td>ER and Hospitalization costs*</td>
<td>1021 (209)</td>
<td>434 (106)</td>
<td>416 (94)</td>
</tr>
<tr>
<td>Specialist costs**</td>
<td>228 (21)</td>
<td>330 (27)</td>
<td>311 (18)</td>
</tr>
<tr>
<td>Total Out-of-Pocket Costs borne by families</td>
<td>3174 (858)</td>
<td>3434 (658)</td>
<td>5062 (1168)</td>
</tr>
<tr>
<td>Medication costs***</td>
<td>171 (26)</td>
<td>275 (30)</td>
<td>366 (44)</td>
</tr>
<tr>
<td>Special food costs</td>
<td>744 (216)</td>
<td>941 (230)</td>
<td>1545 (347)</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001 for F-test of equality of means across groups.
### Racial/Ethnic Cost Disparity

<table>
<thead>
<tr>
<th>Mean Annual Costs (SE), US$</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Direct Costs borne by health care system</strong>*</td>
<td>999 (104)</td>
<td>493 (109)</td>
<td>643 (224)</td>
<td>885 (514)</td>
</tr>
<tr>
<td><strong>ER and Hospitalization costs</strong>*</td>
<td>504 (79)</td>
<td>108 (60)</td>
<td>395 (220)</td>
<td>1271 (630)</td>
</tr>
<tr>
<td><strong>Specialist costs</strong>*</td>
<td>310 (13)</td>
<td>157 (40)</td>
<td>127 (37)</td>
<td>101 (36)</td>
</tr>
<tr>
<td><strong>Total Out-of-Pocket Costs borne by families</strong>*</td>
<td>4203 (750)</td>
<td>395 (452)</td>
<td>1093 (856)</td>
<td>1327 (1,948)</td>
</tr>
<tr>
<td><strong>Medication costs</strong>*</td>
<td>312 (28)</td>
<td>52 (18)</td>
<td>148 (78)</td>
<td>87 (37)</td>
</tr>
<tr>
<td><strong>Special food costs</strong>*</td>
<td>1213 (200)</td>
<td>177 (501)</td>
<td>219 (281)</td>
<td>148 (290)</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001 for F-test of equality of means across groups.

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### Why Choose Therapy

- Food allergy affects 8% of children
  -- Direct/Indirect cost of $24.8B/yr
  -- Personal cost of $4,184/patient/yr
- No known cure or treatment
- Nut, seed, seafood allergies lifelong and severe
- Reaction severity poorly predictable
- Accidental reactions from trace amounts occur
- Reduced HRQL associated with food allergy

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*Why choose therapy and adapted.
Why Not Choose Therapy

- It’s effect is unproven at best
  --Still in phase II→III, cannot predict who will be successful
  --No proven long term clinical or immunologic effects
  --Unclear outcomes, duration of therapy, long term costs
- Highly subjective designation of safe
  --High % of participants react, reaction severity worsens
  --Some develop EoE (possibly a worse disease)
- Not FDA approved, but private practices may offer it
- Are risks worth the benefits, considering natural hx?
- Health utility for avoidance as management is 0.9

Decisions to Make

- Is the process of OIT worse than living with disease?
- What are the caregiver goals of therapy
- What are the caregivers trade-offs and relative value of the therapy compared to avoidance
- What are the caregiver health beliefs?”
- How likely does the caregiver think the chances of success are?
- With other potential therapies, is OIT the best choice?
Ottawa Decision Support Framework

- Framework guiding development/evaluation of decision support interventions.
- Participants’ ‘decisional needs’ (e.g., knowledge, values, support) will affect the decision quality (informed, values concordant decisions) which impacts outcomes such as emotions (regret, blame), behavior, and use of health services.
- Stakeholders include caregivers, family members, and clinicians.
- The framework asserts that decision support can improve decision quality by addressing unresolved ‘decisional needs.’

Principles of Shared Decision Making

- Develop a partnership with the patient.
- Establish or review the patient’s preference for information, e.g., amount and format.
- Establish or review the patient’s preferences for role in decision-making.
- Ascertained and respond to patients’ ideas, concerns, and expectations.
- Identify choices and evaluate the research evidence in relation to the individual patient.
- Present (or direct to) evidence, taking into account the above steps, and help the patient reflect upon and assess the impact of alternative decisions with regard to their values and lifestyles.
- Make or negotiate a decision in partnership, manage conflict.
- Agree upon an action plan and complete arrangements for follow-up.
Coaching a Shared Decision

Pros of Therapy
- Affects 8% of children
  --$24.8B/yr, $4,184/patient/yr
- No cure or treatment, some allergies lifelong
- Reaction severity poorly predictable
- Reduced HRQL associated with food allergy
- WTP of ~$3500/child
- Multiple options, hot area of focus/funding

Cons of Therapy
- Effect is unproven
  --Still in phase II→III
  --Cannot predict success
  --Unclear outcomes, duration, costs
- Safety is subjective
  --High OIT% react
  --Reaction severity worsens, EoE develops
- Not FDA approved, but offered in some practices
- Are risks worth the benefits?
- Avoidance health utility=0.9
More Decisions to Make

• Is the process of OIT worse than living with disease?
• What is the bill of goods sold to parents?
• Why would a parent enroll their child?
  --High risk therapy, but disease is not fatal
  --Health utility for avoidance as option is very high
• Who is an optimal candidate
• Is therapy even cost-effective—biggest unknown!
• With multiple therapies, which is the best choice?
• What are caregiver goals and preferences?

Conclusions

• Entering therapy a very complex decision
• Highly personal, based on preferences and trade-offs acceptable to caregiver
• Data support high utility for avoidance, low WTP, risk-averse preferences, but that therapy betters QoL
• Cost-effectiveness of therapy will be crucial to determine
• Providers must learn how to coach a shared decision