Understanding Therapy:
To treat or not to treat, that is the question!

June 5, 2018

Enas el Gouhary & Sheri Keitz
Objectives

✓ Incorporate best evidence about a treatment using evidence cycle

✓ Define Selected Key Concepts in RCT
  • Randomization/Allocation concealment
  • Blinding
  • Intention to treat versus per protocol
  • Treatment effect
The 5 A's

Evidence-based Medicine Cycle

THE PATIENT

ASSESS

ASK

ACQUIRE

APPLY

APPRAISE
You are a pediatrician in a busy office. You meet with Mrs Smith who is a mother of 2 children

Mike is 4 months old and has eczema and her older son is 5 years old and has nuts allergy.

She read on social media that introducing peanut products at 4-6 months decrease the risk of developing peanut allergy.

She asked her G.P. but he was uncomfortable making the recommendation because of the FH of nut allergy. She asks you should she introduce peanut butter to Mike's diet?

To treat or not to treat... that is the question!
21 percent increase in childhood peanut allergy since 2010
More children have food allergies, including more black children

Date: October 27, 2017
Source: American College of Allergy, Asthma, and Immunology
Summary: New research suggests that peanut allergy in children has increased 21 percent since 2010, and that nearly 2.5 percent of US children may have an allergy to peanuts.
One more thing...

Nut allergy boy, 7, suffers two heart attacks after 'teacher hands him chocolate HAZELNUT in class'

Rehan Butt, seven, had a massive allergic reaction after biting into the chocolate and had to be rushed to hospital where he was hooked up to a ventilator to help him breathe
One more thing...

New peanut allergy prevention guidelines start in infancy

By Susan Scutti, CNN
Updated 7:04 AM ET, Thu January 5, 2017

Story highlights

Some infants should be introduced to peanut-containing foods as early as 4 months

Peanut allergy affects about 2% of the children in the United States

A study to snack on

The LEAP trial is significant because it was "the first and only large, randomized prevention trial for peanut allergies," and so the results are considered "definitive," said Dr. Jerry Nepom, director of the Immune Tolerance Network. The network developed the LEAP trial, which was led by professor Gideon Lack.
One more thing...

The fate of the world’s children depends on your ability to pull this off.
THE PATIENT

The 5 A's

ASSESS

Evidence-based Medicine Cycle

APPLY

ASK

ACQUIRE

APPRAISE
Clinical question formation

**P**opulation

**I**ntervention

**C**omparison

**O**utcome

**T**ype of Question

**T**ype of (ideal) study design
Clinical question formation

Preschool Children with eczema

Early introduction of peanut containing diet

Peanut free diet (Avoidance)

Development of peanut allergy

Therapy question

Randomized controlled trial or meta analysis
THE PATIENT

Evidence-based Medicine Cycle

The 5 A's

ASSESS

ASK

ACQUIRE

APPLY

APPRAISE
Search strategy

   PMID: 28719388
   Similar articles

   PMID: 28151740
   Similar articles

   PMID: 27207693
   Similar articles

Effect of Avoidance on Peanut Allergy after Early Peanut Consumption.
PMID: 26942282
   Free Article

((("arachis"[MeSH Terms] OR "arachis"[All Fields] OR "peanut"[All Fields]) AND "early introduction"[All Fields]) AND ("child, preschool"[MeSH Terms] OR ("child"[All Fields] AND "preschool"[All Fields]) OR "preschool child"[All Fields] OR ("child"[All Fields] AND "preschool"[All Fields]) OR "child, preschool"[All Fields])))
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

ABSTRACT

BACKGROUND
The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia. We evaluated strategies of peanut consumption and avoidance to determine which strategy is most effective in preventing the development of peanut allergy in infants at high risk for the allergy.
Orientation to paper (PICOT)

• **P**: 640 children age 4-11 ms with severe eczema, egg allergy or both in a single site in UK from December 2006- May 6, 2009
## Intervention and control

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary peanut regular consumption until 60ms</td>
<td>Avoidance of peanut products until 60ms</td>
</tr>
<tr>
<td>→ open label oral food challenge (OFC)</td>
<td></td>
</tr>
<tr>
<td>→ those with positive reaction → avoid peanuts</td>
<td></td>
</tr>
<tr>
<td>→ included ITT</td>
<td></td>
</tr>
<tr>
<td>→ Adherence assessed with:</td>
<td></td>
</tr>
<tr>
<td>→ validated food-frequency questionnaire</td>
<td></td>
</tr>
<tr>
<td>→ measurement of peanut in bed dust, an objective validated surrogate for consumption</td>
<td></td>
</tr>
</tbody>
</table>
Primary outcomes:
- Proportion of patients with peanut allergy at 60ms of age determined by an oral food challenge

Secondary outcomes included:
- Skin prick test results
- Peanut specific IgE, IgG4 levels
- Adverse events: GI, Urticaria, Respiratory symptoms
The 5 A’s

ASSESS

APPLY

APPRaise

ACQUIRE

Evidence-based Medicine Cycle

THE PATIENT
Critical appraisal

Therapy Worksheet provides framework to assess a Randomized Controlled Trial

<table>
<thead>
<tr>
<th>How serious is the risk of bias?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did intervention and control groups start with the same prognosis?</td>
</tr>
<tr>
<td>Were patients randomized?</td>
</tr>
<tr>
<td>Was randomization concealed?</td>
</tr>
<tr>
<td>Were patients in the study groups similar at baseline with respect to prognostic factors?</td>
</tr>
<tr>
<td>Was prognostic balance maintained as the study progressed?</td>
</tr>
<tr>
<td>To what extent was the study blinded?</td>
</tr>
<tr>
<td>Were groups prognostically balanced at the study’s conclusion?</td>
</tr>
<tr>
<td>Was follow-up complete?</td>
</tr>
<tr>
<td>Were patients analyzed in the groups to which they were randomized?</td>
</tr>
<tr>
<td>Was the trial stopped early?</td>
</tr>
</tbody>
</table>
Goal of randomization

To evenly distribute all **known and unknown** prognostic variables between the groups
Randomization: Part I

Diagram:

- P
- R
- O
- List generation
Randomization

• Participants were **stratified** into 2 study cohorts on the basis of the results of a skin-prick test for peanut allergy
  – No measurable wheel ➔ SPT negative
  – 1 mm-4mm wheel ➔ SPT positive

• Participants in each study cohort were then randomly assigned to:
  – Intervention: dietary peanut
  – Control: peanut avoidance
Randomization and Stratification

Study population

Stratification

Randomization

Skin Prick test negative
- Peanut consumption
- Peanut avoidance

Skin Prick test positive
- Peanut consumption
- Peanut avoidance
Stratification

✅ Stratification: is used to achieve approximate balance of important characteristics without sacrificing the advantages of randomization

✅ Blocking: is used to keep the numbers in each group very close at all times
Goal vs. Outcome of randomization

We may not always achieve this goal.
Back to our paper
Did Randomization Work?

Table 1: baseline demographics
## Table #1

<table>
<thead>
<tr>
<th></th>
<th>Negative Stratum (N=542)</th>
<th>Positive Stratum (N=98)</th>
<th>Overall (N=640)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening (mo, mean (SD))</td>
<td>7.7 (1.71)</td>
<td>7.7 (1.77)</td>
<td>8.4 (1.66)</td>
</tr>
<tr>
<td>Male sex, no. (%)*</td>
<td>174 (64.4%)</td>
<td>148 (54.4%)</td>
<td>34 (66.7%)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>207 (76.7%)</td>
<td>196 (72.1%)</td>
<td>37 (72.5%)</td>
</tr>
<tr>
<td>Black</td>
<td>21 (7.8%)</td>
<td>21 (7.7%)</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>34 (12.6%)</td>
<td>40 (14.7%)</td>
<td>6 (11.8%)</td>
</tr>
<tr>
<td>Asian†</td>
<td>6 (2.2%)</td>
<td>10 (3.7%)</td>
<td>3 (5.9%)</td>
</tr>
<tr>
<td>Chinese, Middle Eastern or other</td>
<td>2 (0.7%)</td>
<td>4 (1.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Severe eczema, no. (%)</td>
<td>236 (87.4%)</td>
<td>246 (90.4%)</td>
<td>48 (94.1%)</td>
</tr>
<tr>
<td>Age at onset of eczema (mo, mean (SD))</td>
<td>2.2 (1.65)</td>
<td>2.3 (1.61)</td>
<td>2.1 (1.60)</td>
</tr>
</tbody>
</table>
Allocation concealment
Allocation Concealment:

• No description of the procedure of randomization thus we cannot determine whether allocation was concealed

• Note: the words “allocation concealment” are almost never stated explicitly in the text

• Kind of things you might see central randomization or computer generated lists
Allocation concealment

✓ The person who is enrolling participants cannot know, predict, or manipulate the list

✓ Trials with inappropriate allocation concealment are associated with larger estimates of treatment effect
Blinding:
Sentence from the paper

• Open-label study
• Participants and parents were aware of assigned group. Could not use placebo.
• Primary outcome assessed by a double-blind placebo
• No information on blinding data collectors or data analysts
Were patients, caregivers, collectors of outcome data, adjudicators of outcome, and data analysts aware of group allocation?

Blinding is masking the group assignment to ensure all groups are treated the same apart from the intervention through the follow up period.

Trials with inappropriate blinding are also associated with larger estimates of effect, but not as much as with inappropriate allocation concealment.
Blinding

P → R → O

List generation  Allocation concealment
Among most common sources of confusion in teaching randomized trials

Why?

Allocation concealment and blinding are both about someone not knowing something
## Allocation Concealment vs. Blinding

<table>
<thead>
<tr>
<th>Allocation Concealment</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who?</td>
<td>Patients, caregivers, Data</td>
</tr>
<tr>
<td></td>
<td>collectors, outcome adjudicators, analysts</td>
</tr>
<tr>
<td>Doesn’t know</td>
<td></td>
</tr>
<tr>
<td>When?</td>
<td></td>
</tr>
</tbody>
</table>
## Allocation Concealment vs. Blinding

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<tr>
<th>Who?</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enroller</td>
<td>Patients, caregivers, data collectors, outcome adjudicators, analysts</td>
<td></td>
</tr>
<tr>
<td>Doesn’t know</td>
<td>The list</td>
<td></td>
</tr>
<tr>
<td>When?</td>
<td>Part of randomization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allocation Concealment</td>
<td>Blinding</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Who?</strong></td>
<td>Enroller</td>
<td>Patients, caregivers, data collectors, outcome adjudicators, analysts</td>
</tr>
<tr>
<td>Doesn’t know</td>
<td>The list</td>
<td>Group assignments</td>
</tr>
<tr>
<td><strong>When?</strong></td>
<td>Part of randomization</td>
<td>Starts once allocated</td>
</tr>
</tbody>
</table>
Back to the paper
How Serious is Risk of Bias?

- Randomized: Yes
- Allocation: Not clear
- Similar at Baseline: Mostly except gender
- Blinding: Not patients or providers (? others) but final primary outcome assessors were blinded
- Follow up: 98% retention rate
- Stopped early for benefit: No
- Intention to treat: Yes*
What are the Results?
Analyzing Results: Concepts

- Intention to Treat
- Lost to Follow Up
- Sensitivity Analysis: Worst Case Imputation
- Per-Protocol Analysis
Intention-to-treat (ITT)

- Intention to treat patients are analyzed in the groups to which they were randomized.
- ITT preserves balance of prognostic factors created by randomization among the groups.
- ITT describes a “real world” effect at a population level; acknowledges that patients do not always adhere.
- Results are an underestimate of likely benefit for fully compliant population.
Intention-to-treat (ITT)

• Hypothetical Trial of surgical vs. medical intervention for stroke prevention in cerebrovascular disease

• Assumptions
  – Constant event rate in each group (i.e. the intervention does not work)
  – Surgical arm includes time for preoperative care or OR access in the operative group
Intention-to-treat (ITT)

Cerebro-vascular disease

Surgery + ASA

ASA

Strok e

100

10

100

10

10

Stroke

Per Protocol

ITT

Surgery

10/90 = 11%

10/100 = 20%

RD = 9%

20/100 = 20%

RD = 0%

20/100 = 20%
What are the Results?
**Intention to Treat**

- 834 Participants were screened for LEAP study
  - 194 Were excluded
    - 76 Had SPT >4 mm
    - 118 Did not have severe eczema
  - 640 Underwent randomization

**Stratified Randomization**

- Skin Test Negative
  - 542 Were in the SPT-negative cohort
    - 270 Were assigned to peanut avoidance
      - 7 Had missing data on outcomes
      - 4 Withdrawn voluntarily
      - 2 Could not be evaluated by means of diagnostic algorithm
      - 1 Had other reason
      - 263 Were included in the ITT analysis
        - 18 Were excluded owing to inadequate adherence to treatment
        - 245 Were included in the per-protocol analysis
    - 272 Were assigned to peanut consumption
      - 271 Consumed peanut protein
      - 5 Had missing data on outcomes
      - 2 Withdrawn voluntarily
      - 1 Was lost to follow-up
      - 2 Had other reasons
      - 266 Were included in the ITT analysis
      - 11 Were excluded owing to inadequate adherence to treatment
      - 255 Were included in the per-protocol analysis

- Skin Test Positive
  - 98 Were in the SPT-positive cohort
    - 51 Were assigned to peanut avoidance
      - 41 Consumed peanut protein
      - 41 Were included in the ITT analysis
      - 2 Were excluded owing to inadequate adherence to treatment
    - 47 Were assigned to peanut consumption
      - 51 Were included in the ITT analysis
      - 6 Had a positive baseline peanut challenge, did not consume peanut, and were included in the ITT analysis
      - 41 Were included in the per-protocol analysis
**Intention to Treat**

**Stratified Randomization**

834 Participants were screened for LEAP study

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640 Underwent randomization

**Skin Test Negative**

<table>
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<tr>
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<th>Included in the per-protocol analysis</th>
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<tr>
<td>542</td>
<td></td>
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<td>245</td>
</tr>
<tr>
<td>270</td>
<td>Avoid</td>
<td>1 Had a positive baseline peanut challenge, did not consume peanut, and was included in the ITT analysis</td>
<td></td>
</tr>
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<td>Consume</td>
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<td>7</td>
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<tr>
<td>4</td>
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</tr>
<tr>
<td>1</td>
<td>Had other reason</td>
<td>1 Had other reason</td>
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**Skin Test Positive**

<table>
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</tr>
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<td>47</td>
<td>Consume</td>
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<td>41 Were included in the per-protocol analysis</td>
</tr>
<tr>
<td>6</td>
<td>Had a positive baseline peanut challenge, did not consume peanut, and were included in the ITT analysis</td>
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</tr>
<tr>
<td>2</td>
<td>Were excluded owing to inadequate adherence to treatment</td>
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</tbody>
</table>

Note: The diagram summarizes the randomization process and the outcomes for participants with positive and negative skin tests, including reasons for exclusion and inclusion in the ITT and per-protocol analyses.
Stratified Randomization

834 Participants were screened for LEAP study

194 Were excluded
   76 Had SPT >4 mm
   118 Did not have severe eczema

640 Underwent randomization

98 Were in the SPT-positive cohort

51 Avoid

51 Were included in the ITT analysis

1 Was excluded owing to inadequate adherence to treatment

50 Were included in the per-protocol analysis

47 Consume

6 Had a positive baseline peanut challenge, did not consume peanut, and were included in the ITT analysis

41 Were included in the ITT analysis

41 Consumed peanut protein

2 Were excluded owing to inadequate adherence to treatment

39 Were included in the per-protocol analysis

0 missing

0 missing
Intention to Treat

Stratified Randomization

Skin Test Negative

542 Were in the SPT-negative cohort

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7 missing

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4 Withdrew voluntarily
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263 Were included in the ITT analysis

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272 Consume

5 missing

271 Consumed peanut protein

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267

11 Were excluded owing to inadequate adherence to treatment

255 Were included in the per-protocol analysis

834 Participants were screened for LEAP study

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5 missing

0 missing

0 missing
Primary Outcome: Peanut Allergy @ 60 mo

A Intention-to-Treat Analysis

SPT-Negative Cohort (N=530)

- Avoidance Group: 13.7%
- Consumption Group: 1.9%
- P < 0.001

SPT-Positive Cohort (N=98)

- Avoidance Group: 35.3%
- Consumption Group: 10.6%
- P = 0.004

Both Cohorts (N=628)

- Avoidance Group: 17.2%
- Consumption Group: 3.2%
- P < 0.001

Skin Test Negative

Skin Test Positive

Both Groups
Primary Outcome: Peanut Allergy @ 60 mo

- Risk Difference (Subtract)
  \[17.2\% - 3.2\% = 14\%\]

- Risk Ratio (Divide)
  \[\frac{3.2\%}{17.2\%} = 0.186\]

- Relative Risk Reduction (Subtract: 1-Risk Ratio)
  \[1 - 0.186 = 0.814 (81\%)\]

- Number Needed to Treat (Divide: 100/ Risk Difference)
  \[\frac{100}{14} = 7.14 \text{ (rounds up to 8 people)}\]

Both Cohorts (N=628)

- Avoidance Group: 17.2%
- Consumption Group: 3.2%

P < 0.001
In Words...

• Risk Difference (risk reduction or risk increase):

The reduction in risk in peanut allergy at 60 months is 14% for the peanut consumption group as compared with the peanut avoidance group.

• Risk Ratio (relative risk):

The risk of peanut allergy at 60 months in the consumption group is a 19% of that in the avoidance group.
Number Needed to Treat

What is the risk difference of 14% telling you?

In order to prevent peanut allergy in 14 pts, you need to offer peanut consumption strategy to 100.

In order to peanut allergy in 1, how many do you need to offer consumption strategy?

Formula
NNT: 100 / RD %
Number Needed to Treat

✔ Formula: \( NNT = \frac{100}{RD} \)
\( NNT = \frac{100}{14\%} = 7.14 \rightarrow 8 \)
\( NNT = 8 \)

✔ Words: You need give peanut exposure to 8 patients in order to prevent one extra peanut allergy at 50 months compared to peanut avoidance.
Relative Risk Reduction

✔ Formula: \( RRR = 1 - \text{Risk Ratio} \)

\[
RRR = 1 - 0.19 \\
RRR = 0.81
\]

✔ Words: The risk of peanut allergy at 60 months in the peanut consumption group is reduced by 81% compared to peanut avoidance strategy.
Primary Outcome: Peanut Allergy @ 60 mo

- Risk Difference (Subtract): $35.3\% - 10.6\% = 24.7\%$
- Risk Ratio (Divide): $10.6\% / 35.3\% = 0.3$
- Relative Risk Reduction (Subtract: 1-Risk Ratio): $1 - 0.3 = 0.7 \ (70\%)$
- Number Needed to Treat (Divide: 100/ Risk Difference): $100 / 25\% = 4 \text{ people}$
Primary Outcome: Peanut Allergy @ 60 mo

A Intention-to-Treat Analysis

SPT-Negative Cohort (N=530)

- Risk Difference (Subtract)
  13.7% - 1.9% = 11.8%

- Risk Ratio (Divide)
  1.9% / 13.7% = 0.14

- Relative Risk Reduction (Subtract: 1-Risk Ratio)
  1 - 0.14 = 0.86 (86%)

- Number Needed to Treat (Divide: 100/ Risk Difference)
  100 / 11.8 = 8.5 (rounds up to 9 people)
Lost to Follow Up

- Different concept than ITT
- If someone is no longer available for assessment (lost to follow up)
- Patients lost to follow up create uncertainty
  - Can use statistical methods to handle missing data and try to predict outcomes if you have some data
  - Can do a sensitivity analysis
  - Can’t just add them to the denominator
- If someone is nonadherent (drop out)
Sensitivity Analysis: Worst Case Imputation

• Sensitivity Analysis: looks at how sensitive the results are to uncertainty of patients lost to follow up

• Worst Case Analysis: assumes outcomes that would be the ‘worst case’ (e.g. patient with the intervention being studied dies and patient in the comparison group is alive)
Worst Case Scenario (ITT)

Stratified Randomization

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118 Did not have severe eczema

640 Underwent randomization

98 Were in the SPT-positive cohort

51 Were assigned to peanut avoidance
47 Were assigned to peanut consumption

0 missing

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Worst Case Scenario (ITT)

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51

47

834 Participants were screened for LEAP study

194 Were excluded
76 Had SPT ≥4 mm
118 Did not have severe eczema

640 Underwent randomization

0 missing

0 missing
Worst Case Scenario: 12 People Missing

Intention to Treat Analysis

Both Cohorts (N=628)
P<0.001

<table>
<thead>
<tr>
<th>Avoidance Group</th>
<th>Consumption Group</th>
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<tbody>
<tr>
<td>17.2%</td>
<td>3.2%</td>
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</tbody>
</table>

ITT: Worst Case Scenario

A total of 12 people added to denominator

Both Cohorts (N=640)
P<0.001

<table>
<thead>
<tr>
<th>Avoidance Group</th>
<th>Consumption Group</th>
</tr>
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<tbody>
<tr>
<td>16.8%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

7 in avoidance group attributed to NO ALLERGY

5 in consumption group attributed to ALLERGY
Worst Case Scenario: 12 People Missing

Intention to Treat Analysis

A total of 12 people added to denominator

Both Cohorts (N=628)
P<0.001

Worst Case Scenario Math

Risk Reduction: 12.1% compared to 14%
Risk Ratio: 0.28 compared to 0.19
RRR: 72% compared to 81%
NNT: 8.26 (9) compared to 7.14 (8)
Per-Protocol

- Analysis in which investigators include only patients that fully followed the trial protocol
  - Not lost to follow up; available for each visit
  - Adherent; followed treatment arm instructions
- In general, fully compliant patients are healthier people with healthier behaviors in either group
- Allows you to explore the best estimate for a highly compliant group of patients
- Does NOT preserve prognostic balance created by randomization
Per Protocol

Stratified Randomization

Skin Test Negative

542 Were in the SPT-negative cohort

270 Were assigned to peanut avoidance
- 7 had missing data on outcomes
- 4 withdrew voluntarily
- 2 could not be evaluated by means of diagnostic algorithm
- 1 had other reason

263 included in the ITT analysis
- 18 excluded

272 Were assigned to peanut consumption
- 5 had missing data on outcomes
- 2 withdrew voluntarily
- 1 was lost to follow-up
- 2 had other reasons

267 were included in the ITT analysis
- 11 excluded

271 consumed peanut protein

7 missing

5 missing

51

47

7 missing

51

47

64 participants were screened for LEAP study

194 were excluded
- 76 had SPT > 4 mm
- 118 did not have severe eczema

62 participants underwent randomization
834 Participants were screened for LEAP study

194 Were excluded
- 76 Had SPT >4 mm
- 118 Did not have severe eczema

640 Underwent randomization

98 Were in the SPT-positive cohort

51 Were assigned to peanut avoidance

47 Were assigned to peanut consumption

51 Were included in the ITT analysis

6 Had a positive baseline peanut challenge, did not consume peanut, and were included in the ITT analysis

41 Were included in the ITT analysis

41 Consumed peanut protein

0 missing

1 Excluded

50 Were included in the per-protocol analysis

39 Were included in the per-protocol analysis

6 + 2 Excluded
Per-Protocol: 39 People Nonadherent

Intention to Treat Analysis

Both Cohorts (N=628)

P<0.001

Per Protocol

A total of 39 people taken out

Both Cohorts (N=589)

P<0.001
Per-Protocol: 39 People Nonadherent

Intention to Treat Analysis

Both Cohorts (N=628)
P<0.001

Risk Reduction: 17% compared to 14%
Risk Ratio: 0.017 compared to 0.19
RRR: 98% compared to 81%
NNT: 5.8 (6) compared to 7.14 (8)

Per Protocol

A total of 39 people taken out

Both Cohorts (N=589)
P<0.001

Per-Protocol Math

Risk Reduction: 17% compared to 14%
Risk Ratio: 0.017 compared to 0.19
RRR: 98% compared to 81%
NNT: 5.8 (6) compared to 7.14 (8)
Evidence-based Medicine Cycle

The 5 A’s

ASSESS

ASSESS

ASK

APPRaise

ApplY

AcQuire

The Patient
You are a pediatrician in a busy office. You meet with Mrs Smith who is a mother of 2 children.

Mike is 4 months old and has eczema and her older son is 5 years old and has nuts allergy.

She read on social media that introducing peanut products at 4-6 months decrease the risk of developing peanut allergy.

She asked her G.P. but he was uncomfortable making the recommendation because of the FH of nut allergy. She asks you should she introduce peanut butter to Mike's diet?

To treat or not to treat... that is the question!
Back to our Scenario...

✓ Raise hands: how many would consider an early introduction of dietary peanut?

✓ How many would consider obtaining more information/tests?

✓ How many will recommend against early introduction of peanut products?
Applicability

✓ Were the study patients similar to my patient?

Yes but:
- they excluded patients with highly positive skin test >4mm
- those with positive oral food challenge test were advised to avoid peanut
Were all patient-important outcomes considered?
Adverse event volcano plot
**Applicability**

- Are the likely benefits worth the potential harms and costs?

- Patients with high risk for peanut allergy will likely need a referral to an allergist for SPT and/or Oral challenge test -> increased cost/resources

- On the other hand, early introduction of peanut to 8 patients to prevent one patient from developing peanut allergy
Back to our case

- referral to allergist for skin prick test/OFC for consideration to start early introduction of peanut products

- Counselling about chocking hazards with peanut

- Counselling about risks of exposure for sibling with nut allergy
Take-home points

✓ Randomization intends to equally distribute prognostic factors between groups.

✓ Multiple factors may threaten the equal prognosis that we seek to achieve through randomization:
  
 ✓ Play of chance (small sample size)
  ✓ Improper allocation concealment
  ✓ Not following intention to treat (for small groups)
Take-home points

- Stratification and blocking are about making the list.

- Allocation concealment is about the enroller not being able to know, predict, or manipulate the random list during enrollment.

- Blinding is a later step (after allocation) that prevents 5 important groups from being able to treat patients differently based on their group allocation.
Take-home points

✓ Therapy math:
  ✓ Subtract (Absolute Risk Difference)
  ✓ Divide (Risk Ratio)

✓ Number Needed to Treat = 100/Risk Difference (%)
✓ Relative Risk Reduction = 1 – Risk Ratio
Take-home points

This is just the beginning...

And also the END...
Thank you!