Latex Allergy
The Last Chapter?

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Disclosures
• No current funding in the field of latex allergy
• Past latex allergy grant funding from:
  – NIOSH-CDC
  – Ansell International (a glove manufacturer)
  – Regent Medical (a glove manufacturer)
• Advisory Board – American Latex Allergy Association
• Past consultant without current activity:
  – Ansell scientific advisory group
  – Regent Medical’s advisory group
  – C. R. Bard medical division

A Question
Thirty (30) years after the first case describing latex allergy is published, is there direct evidence to support that Latex Allergy is caused by exposure to latex gloves?

1. YES?
2. NO?
3. I am unsure?

A Question
1. YES?
2. NO?
3. I am unsure?
Educational Objectives

• Review the history of latex allergy

• Review whether the problem of latex allergy has been resolved

• Present a final study that may definitively tell us if the epidemic of latex allergy was caused by latex glove exposure

NATURAL RUBBER LATEX
Latex – Why Do We Need It?

- Most effective barrier
  - H2O
  - Virus
  - Bacteria
  - Blood
- Tear resistant
- Best elasticity compared to synthetics
- Modulus – ability to be deformed but return to original shape

Latex Components

- Cis 1,4 polyisoprene 70%
- Water 27%
- Protein 2%
  - >240 peptides
  - >50 allergenic proteins
  - 13 well characterized allergens
- Organic/Inorganic materials 1%

Natural Rubber Latex

Latex Allergy
Dry Coagulated Rubber

88% of Latex Use
Latex Allergy
Dipped Rubber

LATEX ALLERGY

- Dipped rubber products have higher allergen content
  - Lower heat vulcanization
  - Shorter heat vulcanization time
- Most clinical reactions to latex are due to contact with dipped rubber products

Latex Allergy - Dermatitis

- Irritant dermatitis often precedes the development of Latex Allergy
- Irritant dermatitis has many causes:
  - Hand washing
  - Glove powder
  - Soaps

Latex Allergy - Contact Dermatitis

- May precede development of latex allergy in some cases
- Causes include:
  - Thiurams
  - Mercaptobenzothiazole
  - Latex proteins ???

Latex Allergy

- IgE mediated
- May or may not have dermatitis
- Protein allergens
- Specific risk groups
- Those risk groups display different reactivity patterns to allergens!
- Genetic determinants may be involved

Latex Allergy Studies

1979-1989
Clinical presentation

1989-1999
Allergen identification
Prevention strategies
Prevalence studies

2000 - 2009
Little new information
Proof of epidemic caused by latex gloves – speculation
LATEX ALLERGY
POSSIBLE CAUSES
• Universal / Standard Precautions
• Marked increase in exposure to latex gloves
  – e.g. exam gloves
  – Higher allergen content of finished products
• Consumer sources of latex (40 K products)
  – Infant pacifiers, household gloves???
• Exposure in individuals already sensitized
  (e.g. fruit allergic subjects)

Allergen Sensitization & Symptoms
• Atopic (genetics)
• Exposure to small but sufficient quantity
  of allergen to develop IgE response
• Re-exposure to an environment that
  elicits symptoms

Latex Glove Sales In USA

LATEX ALLERGY
The Background
1927
1974-1997
1979

• 1927 – German literature describes laryngeal
  edema, urticaria, and asthma
• 1979 – British (Nutter): describes intense
  hand pruritis with exposure to latex glove
• 1980 – Denmark (Förström): allergic rhinitis
  (with urticaria)
• 1984 – Finland (Turjanmaa): anaphylaxis in
  HCW
**LATEX ALLERGY**

- 1987 – Sweden (Axelsson) – anaphylaxis in non-HCW
- 1987 – First HCW prevalence study by Turjanmaa (3% OR personnel)
- 1988 – Seaton – Occupational asthma

**Latex Allergy**

- 1988 Brehler (Germany) identifies plant cross reactivity (fig) and latex
- 1989 Leynadier (France) identifies cross-reactivity of foods and latex
- 1990’s – Multiple authors from Europe, Japan, Canary Islands, Canada, and the US confirm the cross-reactivity of latex and various fruits

**Patients with Spina Bifida**

- 1989 – 2 separate case reports of allergic reactions to latex
  - Slater (USA)
  - Gerber (Switzerland)

**Spina Bifida**

- 1990 – Children’s Hospital of Wisconsin
- 11 severe episodes of anaphylaxis in ten SB patients in the operating room
- 500-fold increase rate of anaphylaxis compared to expected rate
- 1991 – MMWR (Kelly et. al.)

**Spina Bifida**

- All 10 Spina Bifida children were SPT+ to Latex
- Elective surgery stopped in US on SB subjects
- Subsequent investigation with CDC – IV BURETROL SYSTEM containing in-line valves implicated (Kelly et.al. 1994, JACI)
- CDC Survey – multiple cases in US Children’s Hospitals

**Latex Fruit Syndrome**

- 1987 – First HCW prevalence study by Turjanmaa (3% OR personnel)
**LATEX ALLERGY**

Other Epidemic Clusters

- 1991 (Ownby) – Barium enema balloon
- 1987 – 1997 - numerous authors confirm HCW at risk of reactions to latex gloves
- 1990 – Tarlo (Canada) – occupational asthma in glove manufacturing plant

**LATEX ALLERGY**

CLINICAL MANIFESTATIONS

- Urticaria
- Angioedema
- Rhinitis
- Conjunctivitis
- Asthma (occupational)
- Anaphylaxis

**Latex Allergy**

Who is at High Risk?

- Spina Bifida
- Healthcare workers
- Highly exposed
- Atopic
- Many surgeries
- Neonates
- Mechanical ventilation
- General population (?)

**Latex Allergy – 1990’s**

- Multiple relevant allergens (Hev b 1-13)
- Severe untoward reactions to skin tests
- Fruit and latex with common cross-reacting allergens
- Successful care of patients with latex allergy in hospitals
- Occupational asthma associated with cornstarch powder as a carrier of allergenic proteins
**Latex Allergens – Complexity**

- 1992 – Mäkinen-Kiljunen identifies neo-antigen in latex glove not found in natural rubber
- 1993 – Kekwick reviews the changes in polypeptides resulting from storage and processing
- 1993 – Kelly identifies significant risk of anaphylaxis from skin testing to latex

**LATEX ALLERGY - SKIN TEST**

Clone 600 @ 100 µg/ml

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Systemic reactions</th>
<th>Delayed Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>95%</td>
<td>16.1%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Hamilton et al. JACI 1998

2007 – no FDA cleared SPT in US despite the incredible diligence of Dr. Hamilton and Greer!

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**Latex Allergy – Serologic Testing**

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>AlaSTAT</th>
<th>HyTec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>76.3%</td>
<td>73.3%</td>
<td>91.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>96.7%</td>
<td>97.2%</td>
<td>73.3%</td>
</tr>
<tr>
<td>False Negative</td>
<td>24%</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>False Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hamilton JACI 1999

**Latex Allergy**

**Powdered Latex Products**

- Cornstarch Powder Carries Latex Proteins

**Latex Allergy**

**Occupational Asthma Examples**

- Latex allergy 13/273
- Rhinitis 12/13
- Asthma - glove 5/13
- Inhalation challenge positive 7/12
- Bronchial hyper responsive 12/12 (1 declined testing)

Vandenplas O: Am J Respir Crit Care Med 1995
Latex Allergy

Occupational Asthma Examples

- Nurses with latex allergy 6/6
- SPT+/RAST+ 6/6
- Glove challenge asthma 2/6
- Glove challenge rhinoconjunctivitis 4/6
- Inhalation challenge asthma 4/6
- Asthma after glove exposure removed 3/6

Brugnami G; JACI 1995

Question in 2000-2009

Is Latex Allergy Gone?

Publications on Latex Allergy

A surrogate marker for the end of an epidemic?

Lag of observation to publication may be 3 years

Asthma after glove exposure removed

Brugnami G; JACI 1995

Latex Allergy Prevention

- Multiple prevalence studies show lower numbers of sensitized HCW since mid 1990’s with the advent of powder free low allergen gloves to the market
- 2002 – Nieto (Spain) – reduced sensitization in spina bifida
- The factors involved in decline determined by association but not cause and effect

Reduction of Latex Related OA

- 1998 – 2001
- Three (3) longitudinal incident studies
- Inconclusive cause and effect relationship between latex gloves and sensitization!

Courtesy of Dr. Henning Allmers
Latex Allergy – HCW
3 Reasons For Reduced Prevalence

• Less Sensitization (reduced new cases)
• Loss of Sensitization (reduced old cases)
• The “Healthy Survivor” effect (can’t measure it because the HCW left work)

Why Latex Allergy Is Not Gone

• Allergen content of latex gloves declined over 100 fold in the 1990’s
• Less than 50% of latex gloves in US are now powder free
• However, allergic symptoms and sensitization are a function of crossing a critical threshold of exposure

Latex Glove Sales In USA

<table>
<thead>
<tr>
<th>Year</th>
<th>Non sterile gloves</th>
<th>Sterile gloves</th>
<th>Surgeon's gloves</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>1990</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>2000</td>
<td>25</td>
<td>30</td>
<td>35</td>
</tr>
</tbody>
</table>

Latex Allergy - General Population

• Skin test prevalence in Finnish and Italian selected and unselected children: 1%
• 1996 (Ownby) : 6.4% serology
• 2000 (Saxon) : 5.4 - 7.6% serology
• 2002 (Gryzbowski) : 8.2% serology (positive tests done in duplicate)

WHY? – My Opinion

• Testing not accurate? - unlikely
• False Positive? – unlikely but possible
• Prevalence of antibody does not imply clinical reactivity – higher likelihood
• Food and Pollen in vitro cross-reactivity – higher likelihood
• Low level of anti-latex IgE due to exposure to common latex epitopes from many sources - possibly

Latex Allergy

• Proof of concept that latex gloves are the predominant cause IgE sensitization to latex allergen in HCW
• Without the following study, we risk returning to the early 1990’s when as high as 17% of HCW in the US were symptomatic and unable to work
Hypothesis: Latex Gloves Sensitize Health Care Workers to Latex

- Study the baseline incident rate of conversion
- Environmental change – No Powder and Low Allergen gloves
- Rate of Sensitization is the same when airborne latex is detectable

Study Subjects

- Preferentially recruited atopic subjects
- Follow the same HCW population longitudinally through the environmental glove change
- Female workers predominate in hospitals
- All personnel (including all surgeons) agreed to participate in change

Incidence of Latex Allergy in HCW Before and After Glove Interventions

- Study partially reported at AAAAI meeting
- 2 Hospitals (A and B)
- Different glove use characteristics at baseline
- Informed consent
- Questionnaire
- Serial Skin and Serologic testing to latex
- Baseline atopic status by SPT

Study Design

- All subjects skin prick tested serially by the same individual to avoid bias
- Clone 600 latex allergen
- Serial latex serological assays (3 methods)
- Testing every 12 months
- Subjects tested twice before glove intervention
- Subjects serially tested up to four years

Incidence of Latex Allergy in HCW Before and After Glove Intervention

- 90% of glove use in hospitals was exam gloves by buying records
- Evidence of latex aeroallergen in both hospitals despite synthetic exam gloves at one hospital
- Latex allergen related to pre-packaged kits in Hospital A despite other exam gloves latex-free

Example of kits with latex gloves

Note: warning
Glove Use in Hospitals at Baseline
Aeroallergen in HVAC System

<table>
<thead>
<tr>
<th>Surgeon Gloves</th>
<th>Exam Gloves*</th>
<th>Kits with gloves prepackaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powdered Latex</td>
<td>Synthetic</td>
<td>Powdered Latex</td>
</tr>
<tr>
<td>Powdered Latex</td>
<td></td>
<td>* 90% glove use</td>
</tr>
</tbody>
</table>

Study Design – Glove Intervention

<table>
<thead>
<tr>
<th>Hospital A (An aeroallergen change)</th>
<th>Hospital B (skin &amp; aeroallergen change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kits - synthetic glove</td>
<td>Kits – no change</td>
</tr>
<tr>
<td>Exam gloves – synthetic</td>
<td>Exam gloves – powder free latex</td>
</tr>
<tr>
<td>Surgeon gloves – powder free and powdered latex</td>
<td>Surgeon gloves – powder free latex</td>
</tr>
</tbody>
</table>

Results

Prevalence of SPT+ Subjects at the Beginning of the Study*

<table>
<thead>
<tr>
<th>Hospital A</th>
<th>Hospital B</th>
</tr>
</thead>
<tbody>
<tr>
<td>18/305 (5.9%)</td>
<td>21/500 (4.2%)</td>
</tr>
</tbody>
</table>

* P = 0.28 (NS)

Pre-Intervention Initial 12 months
7 Conversions of SPT(-) to SPT(+)

<table>
<thead>
<tr>
<th>Hospital A</th>
<th>Hospital B</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 SPT+</td>
<td>21 SPT+</td>
</tr>
<tr>
<td>256 SPT-</td>
<td>479 SPT-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital A</th>
<th>Hospital B</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 SPT+ (+5 conversions)</td>
<td>21 SPT+ (+2 conversions)</td>
</tr>
<tr>
<td>256 SPT-</td>
<td>479 SPT-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital A</th>
<th>Hospital B</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/709</td>
<td>15/451</td>
</tr>
<tr>
<td>14/258</td>
<td>7/142</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital A</th>
<th>Hospital B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/14</td>
<td>3/16</td>
</tr>
<tr>
<td>0/237</td>
<td>0/422</td>
</tr>
</tbody>
</table>

Results – Post Intervention
4 Conversions (SPT+ to SPT-)

<table>
<thead>
<tr>
<th>Pre-change</th>
<th>Hospital A</th>
<th>Hospital B</th>
<th>A + B</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPT + to –</td>
<td>0/15</td>
<td>0/14</td>
<td>0/29</td>
</tr>
<tr>
<td>SPT - to +</td>
<td>2/258</td>
<td>5/451</td>
<td>7/709</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-change</th>
<th>Hospital A</th>
<th>Hospital B</th>
<th>A + B</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPT + to –</td>
<td>1/14</td>
<td>3/16</td>
<td>4/30</td>
</tr>
<tr>
<td>SPT - to +</td>
<td>0/237</td>
<td>0/422</td>
<td>0/659</td>
</tr>
</tbody>
</table>
Pre Vs. Post Intervention Analysis

- SPT(+) to SPT(-)  
  0/29 vs. 4/30  
  Chi sq = 4.15  
  p = 0.042

- SPT(-) to SPT(+)  
  7/709 vs. 0/659  
  Chi sq = 6.54  
  p = 0.011

Incident Rates of Conversion

- Pre-Intervention  
  SPT(+) to SPT(-)  
  8.2/10,000 person months  
  1 conversion in every 101 SPT(-) workers per year

- Post-Intervention  
  SPT(+) to SPT(-)  
  111.1/10,000 person months  
  1 conversion to SPT- in every 7.5 SPT(+) workers per year

HCW Who Left Their Jobs Within 2 years of Skin Testing

<table>
<thead>
<tr>
<th></th>
<th>SPT (+)</th>
<th>SPT(-)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital A</td>
<td>6/20</td>
<td>47/287</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>(30%)</td>
<td>(16.3%)</td>
<td></td>
</tr>
<tr>
<td>Hospital B</td>
<td>11/26</td>
<td>52/479</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(42.3%)</td>
<td>(10.8%)</td>
<td></td>
</tr>
<tr>
<td>A plus B</td>
<td>17/46</td>
<td>99/766</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(36.9%)</td>
<td>(12.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- latex Allergy in HCW is caused by latex gloves probably through aeroallergen exposure

- HCW with latex allergy are more likely to leave employment (healthy survivor)

A special thanks to many people I have worked and debated this issue with over the years!

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My patients!
Questions?