Medical and Epidemiologic Overview of Beryllium Sensitization and Chronic Beryllium Disease

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Chronic Beryllium Disease

- Chronic lung disorder:
  - immune over-reaction to beryllium
  - Develops in < 3 months to > 30 years
  - Preventable with exposure control
  - Treatable but not curable
  - Goal: Early disease detection to avoid severe disease
How does beryllium disease develop?

Exposed individuals develop an immune response to beryllium

- Inhalation of beryllium dust
- Cells in the blood and lung proliferate (BeLPT)
- Inflammatory response is initiated
- Eventually, scarring or granulomas may result
How often does CBD occur?

- Beryllium Sensitization (BeS) precedes disease: Prevalence <1-20%
- Chronic Beryllium Disease: Prevalence <1-16%
- Of those with abnormal blood BeLPT 20 –100% have CBD at time of initial evaluation
- Those sensitized progress into disease: 6 - 8% per year
- Not known whether in all cases of BeS results in disease, but risk is high
Scope of the Problem

• Beryllium use, potential for exposure, and disease risk
  – Industrial Use
    • Both Primary and “downstream users”
    • Company and it’s subcontractors
    • Current workers and Former workers
  – Communities
Who is at Risk?

- High risk groups:
  - Beryllium machinists
  - Beryllium ceramics workers
  - Dust disturbers
  - Trades workers

- Also at risk:
  - Bystanders, security guards, front office workers, contract workers
  - Community members

- Routes of Exposure:
  - Inhalation
  - Skin
Determination of Risk

BERYLLIUM EXPOSURE + YOUR GENES → BeS & CBD

NOT RELATED
Age
Ethnicity
Gender
Allergies
Epidemiologic Studies in Chronic Beryllium Disease

- Population-based prevalence studies: defining disease risk factors
- Population-based exposure studies
- Population-based genetic studies
- Clinical epidemiologic studies
Prevalence Studies

- BeLPT screening defined the rates of BeS and CBD in beryllium-exposed workforces.
- Hypothesis generating for exposure and genetic studies.
- Clinical components identified rates of CBD among those with BeS.
## Prevalence Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Industry</th>
<th>n</th>
<th>BeS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kreiss, J Occup Med 1989</td>
<td>Be Machinists</td>
<td>51</td>
<td>6/51 11.8%</td>
</tr>
<tr>
<td>Kreiss Am Rev Respir Dis 1993 (1)</td>
<td>Nuclear workers</td>
<td>895</td>
<td>18/895 2.0%</td>
</tr>
<tr>
<td>Kreiss, J Occup Med 1993 (2)</td>
<td>Ceramics</td>
<td>505</td>
<td>9/505 1.8%</td>
</tr>
<tr>
<td>Kreiss, Am J Ind Med 1996</td>
<td>Beryllia Ceramics</td>
<td>136</td>
<td>8/136 5.9%</td>
</tr>
<tr>
<td>Stange, Environ Health Perspect 1996</td>
<td>Nuclear workers</td>
<td>4,268</td>
<td>101/4,268 2.4%</td>
</tr>
<tr>
<td>Kreiss JOEM, 1997</td>
<td>Be production</td>
<td>627</td>
<td>59/627 9.4%</td>
</tr>
</tbody>
</table>
## Prevalence Studies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Industry</th>
<th>n</th>
<th>BeS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stange, Appl Occup Environ Hyg 2001</td>
<td>Nuclear workers</td>
<td>5173</td>
<td>235/5173 4.5%</td>
</tr>
<tr>
<td>Newman, JOEM 2001</td>
<td>Precision machinists</td>
<td>235</td>
<td>22/235 9.4%</td>
</tr>
<tr>
<td>Henneberger, Int Arch Occup Envir Health 2001</td>
<td>Beryllia Ceramics</td>
<td>151</td>
<td>15/151 9.9%</td>
</tr>
<tr>
<td>Duebner, App Occup Environ Hyg 2001</td>
<td>Mining/Extraction</td>
<td>75</td>
<td>4/75 5.3%</td>
</tr>
<tr>
<td>Sackett, JOEM, 2004</td>
<td>Nuclear Clean-up Workers</td>
<td>2,221</td>
<td>19/2221 0.8%</td>
</tr>
<tr>
<td>Welch, Am J Ind Med 2004</td>
<td>Construction Trades Workers</td>
<td>3,842</td>
<td>53/3842 1.4%</td>
</tr>
</tbody>
</table>
## Prevalence Studies (continued)

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<tr>
<th>Study</th>
<th>Industry</th>
<th>n</th>
<th>BeS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenman, Environ Health Perspect, 2005</td>
<td>Beryllium Processing Facility</td>
<td>577</td>
<td>84/577 14.6%</td>
</tr>
<tr>
<td>Schuler, AJIM, 2005</td>
<td>Copper-beryllium Alloy facility</td>
<td>153</td>
<td>16/153 10.4%</td>
</tr>
<tr>
<td>Stanton, JOEM, 2006</td>
<td>Copper-Beryllium Distribution Center</td>
<td>88</td>
<td>1/88 1%</td>
</tr>
<tr>
<td>Rodrigues, AJIM, 2008</td>
<td>Nuclear test site</td>
<td>1,786</td>
<td>23/1,786 1.3%</td>
</tr>
<tr>
<td>Taiwo, JOEM, 2008</td>
<td>Aluminum Smelter Workers</td>
<td>734</td>
<td>2/734 0.27%</td>
</tr>
</tbody>
</table>
Percent of BeS with CBD

Published Study

Kreiss et al 1989
Kreiss 1993 (1)
Kreiss et al 1993 (2)
Kreiss, et al 1996
Stange et al, 1996
Kreiss et al 1997
Stange et al 2001
Newman et al, 2001
Henneberger et al 2001
Welch et al 2004
Rosenman et al 2005
Schuler et al 2005
# Process-related risks of BeS and CBD

<table>
<thead>
<tr>
<th>Study</th>
<th>Process</th>
<th>BeS (%)</th>
</tr>
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<tr>
<td>Kreiss (Am Rev Repir Dis, 1993)</td>
<td>Nuclear Workers</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td>Machinists</td>
<td>4.7%</td>
</tr>
<tr>
<td></td>
<td>Metallurgical operator</td>
<td>4.6%</td>
</tr>
<tr>
<td>Kreiss, (J Occup Med 1993)</td>
<td>Ceramics Workers</td>
<td>1.8%</td>
</tr>
<tr>
<td></td>
<td>R&amp;D/engineering</td>
<td>13.6%</td>
</tr>
<tr>
<td></td>
<td>Ventilation maint.</td>
<td>11.1%</td>
</tr>
<tr>
<td></td>
<td>Dry pressing</td>
<td>15.8%</td>
</tr>
<tr>
<td>Kreiss, (Am J Ind Med 1996)</td>
<td>Beryllia Ceramics</td>
<td>5.9%</td>
</tr>
<tr>
<td></td>
<td>Machining</td>
<td>14.3%</td>
</tr>
<tr>
<td></td>
<td>Lapping</td>
<td>20%</td>
</tr>
</tbody>
</table>
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<tr>
<td>Kreiss JOEM, 1997</td>
<td><strong>Be production</strong></td>
<td>9.4%</td>
</tr>
<tr>
<td></td>
<td>Ceramics production</td>
<td>11.6%</td>
</tr>
<tr>
<td></td>
<td>Be metal production</td>
<td>14.2%</td>
</tr>
<tr>
<td>Stange, Appl Occup Environ Hyg 2001</td>
<td><strong>Nuclear workers</strong></td>
<td>4.5%</td>
</tr>
<tr>
<td></td>
<td>Be Machinists</td>
<td>11.9%</td>
</tr>
<tr>
<td></td>
<td>Health physics</td>
<td>11.9%</td>
</tr>
<tr>
<td></td>
<td>Construction trades</td>
<td>10.0%</td>
</tr>
<tr>
<td>Schuler, AJIM, 2005</td>
<td><strong>Be-copper Alloy</strong></td>
<td>10.4%</td>
</tr>
<tr>
<td></td>
<td>Rod &amp; wire</td>
<td>16.9%</td>
</tr>
</tbody>
</table>
## Serial Surveillance

<table>
<thead>
<tr>
<th>Study</th>
<th>Screening Interval</th>
<th>Number retested</th>
<th># new BeS/CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stange, Environ Health Perspect 1996</td>
<td>3 years</td>
<td>372</td>
<td>10</td>
</tr>
<tr>
<td>Newman, JOEM 2001</td>
<td>Biennial</td>
<td>187</td>
<td>7</td>
</tr>
<tr>
<td>Stange, Appl Occup Environ Hyg 2001</td>
<td>3 years</td>
<td>2891</td>
<td>63</td>
</tr>
<tr>
<td>Hennenberger, Int Arch Occup Environ Health 2001</td>
<td>6 years</td>
<td>76</td>
<td>8</td>
</tr>
</tbody>
</table>
Conclusions from these population based studies

- Overall rates of CBD within these studies range from 0.27% to 14.6%
Conclusions from these population based studies

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• Rates of CBD among those with BeS ranged from 27% to 100%; 14% among short-term workers
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• Identification of elevated process-related risks up to 20%
Conclusions from these population based studies

• Overall rates of CBD within these studies range from 0.27% to 14.6%
• Rates of CBD among those with BeS ranged from 27% to 100%; 14% among short-term workers
• Identification of elevated process-related risks up to 20%
• BeS and CBD among workers with trivial or bystander exposures
Conclusions from these population based studies

• Overall rates of CBD within these studies range from 0.27% to 14.6%

• Rates of CBD among those with BeS ranged from 27% to 100%; 14% among short-term workers

• Identification of elevated process-related risks up to 20%

• BeS and CBD among workers with trivial or bystander exposures

• Serial blood testing identified additional cases of BeS and CBD
Exposure Studies
Exposure Studies

• Estimates of exposure measurements related to development of BeS and CBD
• Exposure estimates were based on work history and collected exposure measurements
• Identification of low-level exposures associated with BeS and CBD
• Generated ideas for different types of exposure quantification and characterization
Exposure Studies

• **Kreiss, Am J Ind Med 1996**
  - beryllia ceramics plant with increased risk among machinists – led to particle size investigations

• **Kelleher, J Occup Environ Med 2001**
  - cumulative exposure was greater for cases compared to controls for total and respirable Be

• **Hennenberger, Int Arch Occup Environ Health 2001**
  - decline in plant wide beryllium exposure was not associated with a decline in sensitization rate

• **Schuler, et al American Journal of Industrial Medicine, 2005**
  - CBD risk was highest in rod and wire production where air levels were the highest.
### Low exposures related to BeS and CBD

<table>
<thead>
<tr>
<th>Study</th>
<th>Industry</th>
<th>Lowest exposures associated with BeS/CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stange, 2001</td>
<td>Nuclear workers</td>
<td>&lt; 0.5 μg/m³</td>
</tr>
<tr>
<td>Kelleher, 2001</td>
<td>Precision machinists</td>
<td>0.02 to 0.1 μg/m³</td>
</tr>
<tr>
<td>Hennenberger, 2001</td>
<td>Beryllia Ceramics</td>
<td>0.05 μg/m³ to 0.06 μg/m³</td>
</tr>
<tr>
<td>Schuler, 2005</td>
<td>Beryllium-copper alloy</td>
<td>&lt;0.01 to 0.33 μg/m³</td>
</tr>
<tr>
<td>Taiwo, 2008</td>
<td>Aluminum Smelter Workers</td>
<td>0.04 to 0.16 μg/m³</td>
</tr>
</tbody>
</table>
Time from first exposure to development of BeS

- Newman et al 2001
  - 6.7% BeS/CBD among 60 workers employed for < 1 year
- Henneberger et al 2001
  - 16% BeS among 37 workers employed for < 1 year
- Both studies also identified individuals who had first abnormal BeLPT up to 40 years after first exposure with previous negative BeLPTs
Conclusions from Exposure Studies
Conclusions from Exposure Studies

• Medical surveillance in concert with exposure data helps identify areas of risk
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• Medical surveillance in concert with exposure data helps identify areas of risk
• BeS and CBD occurs with exposures far below the 2.0 μg/m³ standard
Conclusions from Exposure Studies

• Medical surveillance in concert with exposure data helps identify areas of risk
• BeS and CBD occurs with exposures far below the 2.0 $\mu$g/m$^3$ standard
• Exposures less than 0.1$\mu$g/m$^3$ associated with BeS
Conclusions from Exposure Studies

- Medical surveillance in concert with exposure data helps identify areas of risk
- BeS and CBD occurs with exposures far below the 2.0 $\mu g/m^3$ standard
- Exposures less than 0.1 $\mu g/m^3$ associated with BeS
- Factors that might be important in defining risk:
  - Total exposure
  - Characteristics of beryllium particles
  - Routes of exposure?
Genetic Studies

- Population-based studies have identified genetic risk factors for BeS and CBD
- Genetic studies have contributed to our understanding of mechanism
- The potential use of any genetic marker in differentiating those who will develop CBD from those who will not, should be based on the prevalence of markers within both cases and controls, thus PPV.
# HLA-DPB1 Glu 69 in CBD

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>CBD</th>
<th>CONTROLS</th>
</tr>
</thead>
</table>
| Richeldi, Science 1993  
n= 33 CBD 44 Controls | 97% | 30% |
| Richeldi, Am J Ind Med 1997  
n= 6 CBD 121 Controls | 83% | 30% |
| Wang, J Immunol 1999  
n= 20 CBD 34 Controls | 95% | 45% |
# HLA-DPB1 Glu 69 in BeS and CBD

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>CBD</th>
<th>BeS</th>
<th>CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, Tox 2001</td>
<td>NA</td>
<td>88%</td>
<td>30%</td>
</tr>
<tr>
<td>N= 25 BeS  63 Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saltini, Eur Respir J 2001 *</td>
<td>73%</td>
<td>39%</td>
<td>40%</td>
</tr>
<tr>
<td>N= 22 CBD  23 BeS  93 Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rossman, AJRCCM 2002</td>
<td>84%</td>
<td>90%</td>
<td>47%</td>
</tr>
<tr>
<td>N= 22 CBD  23 BeS  82 Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maier, J Immunol 2003</td>
<td>86%</td>
<td>85%</td>
<td>38%</td>
</tr>
<tr>
<td>N= 104 CBD  50 BeS  125 Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCanlies, Am J Ind Med 2004 *</td>
<td>82%</td>
<td>68%</td>
<td>33%</td>
</tr>
<tr>
<td>N= 90 CBD  64 BeS  727 Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amicosante, Resp Research 2005 *</td>
<td>86%</td>
<td>55%</td>
<td>48%</td>
</tr>
<tr>
<td>N=36 CBD, n=38 BeS, n=86 controls</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What about CBD/BeS in the absence of Glu69?

• Between 15-30 % of BeS and CBD have no Glu69

• In the absence of Glu69, increased frequency of HLA-DRB1*13 in CBD Maier JI 2003, data unpublished

• DRB1*13 glutamic acid at amino acid 71

• In small number of subjects can block proliferation with HLA-DRB1 Fontenot PNAS 2000
# Beryllium: Exposure x Glu69

(Richeldi Am J Ind Med 1997)

<table>
<thead>
<tr>
<th></th>
<th>Machinists (0.9 μg/m³)</th>
<th>Non-Machinists (0.3 μg/m³)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glu69 Pos.</strong></td>
<td>4/16 (25%)</td>
<td>1/25 (4%)</td>
<td>5/41</td>
</tr>
<tr>
<td><strong>Glu69 Neg.</strong></td>
<td>1/31 (3.2%)</td>
<td>0/55 (0%)</td>
<td>1/86</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5/47 (10.6%)</td>
<td>1/80 (1.3%)</td>
<td>6/127 (4.7%)</td>
</tr>
</tbody>
</table>
Genetic Studies

• HLA-DPB1 Glu69: confers increased risk, but is not sufficient, not necessary, for disease
• Multigene disorder—probable role of TGF-β and other polymorphisms
• Genetics and disease progression
• Gene-environment interactions
• Use of gene markers vs. controlling disease through exposure control?
Clinical Epidemiologic Studies
Clinical Epidemiologic Studies

- Validating the use of the BeLPT in medical surveillance
  - Blood BeLPT had high PPV+ for CBD and is efficacious in beryllium medical surveillance (Kreiss, JOM 1993; Stange, Am J Ind Med 2004)
  - Examined PPV+, inter- and intra-laboratory agreement of BeLPT for predicting CBD (Duebner, App Occup Env Hyg 2001)
  - Clinical application of the BeLPT (Barna, Clin Diagn Lab Immunol 2003)
  - Occupational history and BeLPT in the evaluation of patients with sarcoidosis (Fireman, Sarc Vasc Diffuse Lung Dis 2003)
Clinical Epidemiologic Studies

- Identifying physiologic and laboratory based markers in CBD
  - Alterations in gas exchange and the pulmonary vascular bed occur early in CBD (Pappas, ARRD 1993)
  - Beryllium patch test can be used safely to clarify BeS and the diagnosis of CBD (Bobka JOEM 1997)
  - Beryllium-stimulated neopterin as a useful diagnostic adjunct in the non-invasive assessment of CBD (Maier Am J Indus Med 2003)
  - Induced sputum as an evaluation and diagnostic tool for CBD (Lerman, Arch Environ Health, 2003)
Clinical Epidemiologic Studies

• Examining the progression of BeS to CBD
  – BeS progresses to CBD at a rate of 6% – 8% per year. Machining was a risk factor for progression (Newman, ARRD 2004)

• Treatment of CBD
  – Response to long-term corticosteroids in CBD is variable. Lung function improvement after cessation of beryllium exposure (Sood, Chest, 2004)
Future Directions in Epidemiology

- Continued identification of BeS/CBD in other industries, especially related to alloys
- Examination of quantitative and qualitative exposures associated with BeS and CBD.
- Development of new tests for BeS and CBD
- Examine genetic-exposure interactions
- Describe the natural history of CBD
- Evaluation of treatment response in CBD
Thanks to:

- Our patients
- Beryllium workers
- Beryllium Industries
- Agencies that fund our research:
  - NIH
  - CDC/NIOSH
  - U.S. Dept. of Energy
  - U.S. EPA
Questions?