Diagnosis and Management of Beryllium Sensitization and CBD

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“Half of our medical knowledge at any one point is wrong. The problem is that we do not know which half.”
Truth Survival in Clinical Research: An Evidence-Based Requiem?

- Original articles and meta-analyses published from 1945 to 1999 about cirrhosis or hepatitis in adults.
- In 2000, 285 of 474 conclusions (60%) were still considered to be true, 91 (19%) were considered to be obsolete, and 98 (21%) were considered to be false.

The half-life of truth was 45 years.
The Half-life of Truth in Medicine is 45 Years.

• The 20-year survival of conclusions derived from:
  – meta-analysis 57% ± 10%
  – nonrandomized studies 87% ± 2% (P < 0.001)
  – randomized trials 85% ± 3% (P < 0.001).

• The survival of conclusions was not different when studies of high methodologic quality were compared with those of low quality.

• 50-year survival rate was higher for 52 negative conclusions (68% ± 13%) than for 118 positive conclusions (14% ± 4%) (P < 0.001).
Beryllium Properties

- Three times lighter than aluminum (At. Wt. 9/27)
- Seven times stiffer than steel
- High melting point (1285 °C)
- High heat absorption capacity (5 times more than copper)
- Corrosion resistant
- High permeability (transparency) to X-rays
- Lowest neutron absorption cross section of any metal
Beryllium Uses

- nuclear power, ceramics, aerospace, electronics industries, computers, automotive, dental appliances...
Be: An “Admirable” Metal...

“...beryllium is of itself not toxic...it appears that whatever toxicity has been found to occur with the beryllium salts is due to the toxicity of the acid radicals such as fluoride or oxyfluoride, ...or certain salts, such as chloride or sulfate.”


“Beryllium seems to be the Admiral Crichton of metals.... To charge such an admirable metal with having poisonous properties is about as distasteful as accusing a trusted butler of stealing the family plate”.

Acute Beryllium Disease

HOWARD S. VAN ORDSTRAND, M.D. (1911–1988)
Acute Beryllium Disease

- The metal acts as a direct chemical irritant causing a non-specific inflammatory reaction (acute chemical pneumonitis)

- Due to improved industrial hygiene measures, acute beryllium disease has virtually disappeared.
<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>EXPOSURE CONTROLS</th>
<th>BERYLLIUM AIRCOUNTS ($\mu g/m^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>NONE</td>
<td>HIGH (DATA NOT AVAILABLE)</td>
</tr>
<tr>
<td>B</td>
<td>NONE</td>
<td>PEAKS OF 45,000, 83,000 $\mu g$</td>
</tr>
<tr>
<td>C</td>
<td>INSTALLED</td>
<td>FIRST PLANT WITH ENGINEERING CONTROLS PEAKS AT 200 $\mu g$ DURING SHAKE DOWN PERIOD</td>
</tr>
<tr>
<td>D</td>
<td>INSTALLED</td>
<td>PEAKS AT 100 $\mu g$ (ACCIDENTAL - MAINTENANCE WORK)</td>
</tr>
<tr>
<td>E</td>
<td>INSTALLED</td>
<td>PEAKS AT 70 $\mu g$ (FURNACE MALFUNCTIONS)</td>
</tr>
</tbody>
</table>

Cases vs Year

- A: 1940-1950
- B: 1950
- C: 1970
- D: 1980
- E: 1990
Chronic Beryllium Disease

• Chronic beryllium disease (CBD) is a granulomatous disease clinically similar to sarcoidosis.

• Industries where beryllium is manufactured and processed and workers are exposed to beryllium fumes or dust.
CBD Pathophysiology

• A delayed-type hypersensitivity reaction
• Beryllium functions as a hapten and acts as a class II-restricted antigen
• Stimulates local proliferation and accumulation in the lung of beryllium-specific CD+4 T cells.
• Non-specific inflammation
  – changes in lung permeability
  – production of proinflammatory cytokines and growth factors
Natural History of Chronic Beryllium Disease (CBD)

• Exposure → Sensitization → Disease (CBD)
• About 10% of exposed workers get sensitized as determined by a Be-specific lymphocyte proliferation blood test (LPT).
• About 40-50% of sensitized individuals (~5% of all exposed workers) develop CBD as determined by the presence of compatible lung pathology (usually a granuloma).
Exposure

Sensitization

Disease (CBD)
Sensitization

- Evidence of sensitization to Be: a positive lymphocyte proliferation test (LPT) to Be on the blood or bronchoalveolar lavage
- No Lung pathology

DOL:
- a. Beryllium sensitivity. 42 U.S.C. §73841(8)(A) ... A single abnormal LPT/LTT is sufficient to establish beryllium sensitivity ...
Beryllium Specific Lymphocyte Proliferation Test (BeLPT)

- Mononuclear cells (from Blood or BAL)
- Exposed in vitro to beryllium salts
  - Varying concentrations
  - Variable time intervals
- Cell proliferation in the presence of beryllium indicates a positive test.
Exposure

Sensitization

Disease (CBD)
Risk Factors for Sensitization/CBD

- Sensitization and disease development seem to require genetic susceptibility in addition to exposure.
- Exposure: OSHA established 2ug/m³ as acceptable occupational standard (likely not protective).
- Genetic Susceptibility: A variant of the major histocompatibility complex (HLA-DPβ1^{(Glu 69)}): up to 97% of CBD vs 30% of controls
- Factors that determine progression from sensitization to disease are not clear: ? Smoking, ? Race
Cleveland Clinic Cohort

209 sensitized beryllium exposed individuals (+ve blood LPT test)

Demographics
Smoking status
PFTs, ABGs
Bronchoscopy and bx

Controls (n=132)
negative biopsy
(no granuloma)

Cases (n=77)
positive biopsy
(granuloma)
## Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>CBD (n=77)</th>
<th>Controls (BeS) (n=132)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years (mean ± SD)</strong></td>
<td>46 ± 12</td>
<td>43 ± 11</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>63 (82%)</td>
<td>109 (83%)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>14 (18%)</td>
<td>23 (17%)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td>5 (7%)</td>
<td>0 (0%)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Non- African am.</strong></td>
<td>71 (93%)</td>
<td>132 (100%)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td>9 (12%)</td>
<td>43 (33%)</td>
<td>0.0007</td>
</tr>
<tr>
<td><strong>Non-Smoker</strong></td>
<td>68 (88%)</td>
<td>88 (67%)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>
Baseline Pulmonary Function Testing

- Pulmonary function abnormalities were similar among CBD and sensitized (biopsy negative) individuals.
- CBD vs. sensitized (all p=NS):
  - normal spirometry 79% vs. 72%
  - obstruction 12% vs. 17%
  - restriction 9% vs. 11%
  - reduced diffusion capacity 23% vs. 16%
- Subjects who had evidence of obstruction on spirometry or abnormal diffusion capacity were more likely to be smokers (“current” or “ex” smokers) (p= 0.02).
# Effect of Smoking

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>N</th>
<th>CBD</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>111</td>
<td>47</td>
<td>42%</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>45</td>
<td>21</td>
<td>47%</td>
</tr>
<tr>
<td>Active smokers</td>
<td>52</td>
<td>9</td>
<td>17%</td>
</tr>
<tr>
<td>Total</td>
<td>208</td>
<td>77</td>
<td>37%</td>
</tr>
</tbody>
</table>

Odds ratio of CBD for active smokers: 0.61 (p=0.006)
Summary

• In our cohort about 40% of sensitized individuals had CBD.
• Most individuals with CBD have normal pulmonary function tests at the time of initial diagnosis.
• Thus, surveillance / screening for CBD with the BeLPT identifies patients early and enables diagnosis prior to the onset of physiologic abnormalities.
• CBD rates are lower in sensitized individuals who are actively smoking.
• African Americans may be at higher risk of developing CBD once sensitized.
Clinical Manifestations of CBD Are Non-specific

- History: Insidious onset of dyspnea, cough, chest pain, arthralgias, weight loss, and fatigue.
- Exam: Lymphadenopathy, inspiratory crackles, skin lesions, hepatosplenomegaly.
- CXR/CT: Diffuse infiltrates, hilar nodes.
- PFTs: Variable findings: Obstruction, restriction, reduced DLCO.
- In early cases all above could be normal.
CBD Pulmonary Function Tests

- Gas exchange during exercise: most sensitive
- Spirometry: obstruction, restriction or both.
- DLCO declines over the course of the disease.
CBD CXR

• Normal in about half of the patients with documented CBD.

• Abnormal findings in the other half include:
  – hilar adenopathy
  – increased interstitial markings
CBD High Resolution CT (HRCT)

• More sensitive than the CXR.
• Typical findings on HRCT:
  – ground glass opacification
  – parenchymal nodules
  – septal lines.
• HRCT is negative in 25% of patients with documented CBD.
CBD Bronchoscopy

- Needed to make the diagnosis in most patients
- BAL lymphocytosis (> 20% lymphocytes).
- The BeLPT test can also be performed on BAL cells
- Transbronchial biopsies
CBD- Pathology

• The hallmark of CBD is the presence of noncaseating granulomas on lung biopsy
• Histopathologically indistinguishable from sarcoid granulomas (? distribution)
• Other findings (co-morbid pathology):
  – emphysema
  – respiratory bronchiolitis
  – ILD
The Top Four Questions Pulmonologists Ask About Their Beryllium Biopsies

- Did I Get Enough Pieces?
- Did You Look Really Hard for Granulomas?
- Is That a Real Granuloma?
- Did You See Anything Else?
Methods

- Retrospective review by two pathologists
- 240 transbronchial biopsies
  - 80 biopsies positive for granulomas
  - 160 biopsies negative for granulomas
- All slides available:
  - Standard H and E
  - Acid fast
  - Gomorri methenamine silver
- Clinical Data: Chest X-ray, Smoking history, BAL and blood LPT
Percent Positive as a Function of Number of Tissue Fragments

- Number of Tissue Fragments: 2, 3, 4, 5, 6, 7, 8, 9, 10
- Percent Positive: 0% to 60%

The graph shows an increase in the percent positive as the number of tissue fragments increases.
Percent Positive as a Function of Number of Levels

Positive biopsies associated with >20 levels of tissue examined (p<.0002)
Is the Presence of Ill-Formed Granulomas Associated with (+) Clinical Test for CBD?

Well-Formed

Ill-Formed
Is the Presence of Chronic Bronchiolitis associated with Biopsy (+) CBD?

- Chronic bronchiolitis correlated with active or prior smoking history (p<.02)
Summary

• Positive biopsies are associated with
  – abnormal chest x-rays
  – 5 or more pieces of tissue are taken
  – and > 20 levels of tissue are examined microscopically
• Greater number tissue fragments or levels of tissue may be a marker for greater clinical suspicion.
• Well-formed granulomas, but not ill-formed granulomas, are associated with clinical features of chronic beryllium disease.
• Chronic bronchiolitis correlated with active or prior smoking history (p<.02)
Current Diagnostic Criteria for CBD

- Evidence of beryllium sensitization
  - Positive blood LPT
  - Positive BAL LPT

AND

- Evidence of lung pathology (usually a granuloma) on lung biopsy
Beryllium Case Registry (1952-1978)
Diagnostic Criteria for CBD

• Beryllium exposure
  – History of exposure, or
  – Excess beryllium in biologic specimens

• Plus any three of these criteria:
  1. Clinical symptoms of a lower respiratory tract disorder
  2. Reticulonodular infiltrates on chest radiography
  3. Restrictive or obstructive impairment of pulmonary function or a depressed diffusing capacity for carbon monoxide
  4. Histologic demonstration of noncaseating granulomas and/or mononuclear cell interstitial infiltrates on lung biopsy specimens.
Department of Labor Criteria for CBD on or after January 1, 1993

b. Chronic beryllium disease. 42 U.S.C. §73841(13) :

• ... An abnormal LPT ..., together with
• lung pathology consistent with CBD (one or more of the following):
  (a) A lung biopsy showing granulomas or a lymphocytic process consistent with CBD;
  (b) A computerized axial tomography (CAT) scan showing changes consistent with CBD;
  (c) Pulmonary function or exercise testing showing pulmonary deficits consistent with CBD.
Department of Labor Criteria for CBD
Prior to January 1, 1993

• Medical documentation must include at least three of the following:
  - (a) Characteristic chest radiographic or computed tomography abnormalities;
  - (b) Restrictive or obstructive lung physiology testing or diffusing lung capacity defect;
  - (c) Lung pathology consistent with CBD (a.k.a. berylliosis);
  - (d) Clinical course consistent with chronic respiratory disorder;
  - (e) Immunologic tests showing beryllium sensitivity (skin patch or beryllium blood test preferred).
# Summary of Diagnostic Criteria for Chronic Beryllium Disease (CBD)

<table>
<thead>
<tr>
<th></th>
<th>LPT</th>
<th>Bx</th>
<th>Hx of expos.</th>
<th>CXR</th>
<th>PFTs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current Standard</strong></td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Be Registry</strong></td>
<td>-</td>
<td>±</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>± (+ 3/4)</td>
</tr>
<tr>
<td><strong>DOL Before 1-1-93</strong></td>
<td>±</td>
<td>±</td>
<td>*+</td>
<td>±</td>
<td>±</td>
<td>± (+ 3/5)</td>
</tr>
<tr>
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<td>±</td>
<td>*+</td>
<td>±</td>
<td>±</td>
<td>- (+ 1/3)</td>
</tr>
</tbody>
</table>
CBD Treatment

• Team approach is necessary for prevention, screening, early diagnosis, and appropriate treatment of CBD.
  – Industrial hygiene
  – Occupational health
  – Pulmonary specialists

• Cessation of exposure
• Medications

? Natural history?
Cessation of Exposure

• Key component in the management of CBD
• All patients with CBD are advised to avoid further exposure to beryllium.
• No proof that cessation of exposure to beryllium will improve the disease or slow the progression.
Natural History of CBD

- Due to the use of BeLPT, many cases are now diagnosed very early in the course of the disease before radiographic or physiologic changes are seen and before symptoms develop.
Natural History of CBD: Sensitization and Disease

• How many exposed individuals get sensitized?
  10% (3%-15%)

• How many sensitized individuals have CBD at time of initial evaluation?
  50% (20%-80%)

• How many sensitized individuals with neg. initial evaluation develop CBD over time?
  6%/yr (3%-9%)
Beryllium Sensitization Progresses to CBD

Natural History of CBD: Clinical Manifestations

- The natural history of the “disease” is not clear in patients who have granulomas on TBBX but are asymptomatic with no physiologic or radiographic abnormalities.
- How many asymptomatic individuals will develop symptoms over time?
- In a particular individual, can we predict whether the disease will remain stable or progress over time?
CBD-Indications for Therapy

- Presence of symptoms
- Abnormal pulmonary function tests
- Decline in pulmonary function over time.

- In the absence of any of these criteria, no therapy is recommended. Close monitoring of symptoms and follow up pulmonary function testing is recommended.
CBD-Role of Corticosteroids

• Corticosteroids are the treatment of choice.
  – pathogenesis of the disease (immune-mediated)
  – similarities with sarcoidosis

• No controlled studies for CBD therapy are available.
CBD - Role of Corticosteroids

• No consensus on dose or duration
• A three-phase approach:
  – initiation: 40 mg of prednisone daily (or every other day) for 3-4 months.
  – tapering: reduced gradually over 2-6
  – maintenance
• Complete discontinuation is not recommended
Phases of Corticosteroid Treatment of Pulmonary Sarcoidosis

(Judson MA, Chest 1999)
CBD-Other Therapies

• Indications:
  – corticosteroid failure
  – significant side effects from steroids

• Medications that modulate the immune system (lymphocytes)
  – Methotrexate: 5-10 mg per week.
  – Other medications: cyclosporine, azathioprine, cyclophosphamide, ...
  – Tumor necrosis factor (TNF)-α blockers.
Tumor Necrosis Factor (TNF)-α Blockers

- Tumor necrosis factor (TNF)-α is critical in the development and maintenance of granulomatous inflammation.
- Agents developed to inhibit TNF-α have been successful in the treatment of rheumatoid arthritis and inflammatory bowel disease.
- Promising reports in sarcoidosis: trials currently underway.
#1 Lung Transplant Center in the US.
Intermittent vs. Continuous Exposure

- 19 individuals had only intermittent exposure to beryllium:
  - performed contracted work (e.g. electrical, plumbing...etc) at a beryllium processing facility.
  - did not work directly in beryllium production or processing.
- Exposure ranged from 2 months to 20 yrs.
- 16 males, mean age 43±9 yrs.
- All had a positive blood Be-LPTs (beryllium sensitization).
Intermittent vs. Continuous Exposure

- 9 of 16 (47%) had histopathologic evidence of CBD.
- This prevalence of CBD is similar to the other exposure groups.
- The average FVC was 100±18% of predicted, FEV1 100+15% of predicted and DLCO 110±28% of predicted at the time of initial evaluation.
The Half-life of Truth in Medicine is 45 Years.

• The 20-year survival of conclusions derived from:
  – meta-analysis 57% ± 10%
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BeLPT Testing Sites

- Cleveland Clinic Foundation
- Hospital of the University of Pennsylvania
- National Jewish Center for Immunology and Respiratory Medicine
- Specialty Laboratories, Inc.
Summary

• In our cohort about 40% of sensitized individuals had CBD.
• Sensitized individuals with only intermittent exposure to beryllium are at a similar risk of developing CBD compared to workers in more traditional exposure settings.
• Most individuals with CBD have normal pulmonary function tests at the time of initial diagnosis.
• Thus, surveillance / screening for CBD with the BeLPT identifies patients early and enables diagnosis prior to the onset of physiologic abnormalities.
Summary

• CBD rates are lower in sensitized individuals who are actively smoking.
• African Americans may be at higher risk of developing CBD once sensitized.
• The effect of smoking and race on development of sensitization in exposed individuals is not clear.
• NO and CO (and/or other substances) in cigarette smoke may have properties (?anti-inflammatory) that alter the natural history of CBD.
CBD - Role of Corticosteroids

• Long-term use is associated with numerous complications:
  – Hypertension
  – Diabetes
  – Weight gain
  – Osteoporosis
  – Cataracts
  – Glaucoma
  – Fluid retention
  – …etc.
Beryllium-Induced Lung Disease

- Acute chemical pneumonitis
- Chronic Beryllium Disease (CBD), or berylliosis

- Highest Potential for Exposure to Beryllium
  - primary production
  - metal machining
  - reclaiming scrap alloys
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