WASHINGTON STATE DEPT. OF LABOR AND INDUSTRIES
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CLINICAL GUIDELINE FOR THE DIAGNOSIS OF BERYLLIUM SENSITIZATION AND CHRONIC BERYLLIUM DISEASE

PURPOSE

This Guideline provides the clinical diagnostic criteria for beryllium sensitization and chronic beryllium disease (CBD; old term = berylliosis), based on the latest available medical literature and consultation with leading experts in the field. This Guideline does not address exposure prevention, workplace safety, or treatment. In addition, this Guideline is not intended to supplant all adjudicative decisions in cases that meet the case definition and which are crucial to the administration of the Washington workers' compensation system.

BACKGROUND

Beryllium is a lightweight alkaline metal occurring naturally in soils and in coal; [1] it is processed into metals oxides, alloys, and composite materials. [2] It has high strength, light weight, high heat and electrical conductivity, a high melting point, is neutron-moderating and transparent to x-rays, and is non-sparking and non-magnetic.[2-5] Exposure to beryllium usually occurs through the inhalation of beryllium-containing dust, particles, vapor, liquids or fumes, though skin contact can also manifest as dermatitis and ulcerations with poor wound healing. [1] Chronic disease is due to a cell-mediated sensitization response.[2, 6, 7] There is currently no vaccine or post-exposure prophylaxis for beryllium exposure.

ESTABLISHING WORK-RELATEDNESS

Beryllium sensitization and chronic beryllium disease as an industrial injury:
An injury is defined as "a sudden and tangible happening, of a traumatic nature, producing an immediate or prompt result, and occurring from without, and such physical conditions as result therefrom." The only requirement for establishing work-relatedness for an injury is that it occur "in the course of employment."

For example, exposure to beryllium may be an acute, traumatic episode at work, such as a puncture wound from beryllium metal.

Beryllium sensitization and chronic beryllium disease as an occupational disease:
For an occupational disease, establishing work-relatedness requires a more critical analysis that demonstrates more than a simple association between the disease and workplace activities. Establishing work-relatedness for an occupational disease requires all of the following:

a. Exposure: workplace activities that contribute to or cause the condition, such as working in an environment where known beryllium-containing alloys, dust, vapors, or liquids are present.

Certain occupations or work environments that have the potential for exposure to beryllium and beryllium-containing substances are listed in Table 1:

Table 1. Industries and occupations with potential beryllium exposure [2, 8-12]

Industries	Occupations
Atomic energy/nuclear industries including power, weapons & defense	Grinders
Metal working (with Be-containing metals)	Machinists
Rod and wire and copper tubing production	Hot press operators
Aeronautics/aerospace	Welders
Electronics & computers manufacturing	Security Guards where there is known risk of exposure
Construction/demolition	Janitorial workers where there is known risk of exposure
Ceramic manufacturing	Dental hygienists, prosthetists, technicians
Laboratory work	Laser cutters of beryllium metals and alloys
Recycling/Hazardous waste cleanup	Those who worked with fluorescent lamps prior to 1951
Fiber optics	Those who decontaminate or decommission structures where beryllium was present/used.
Dental materials manufacturing and laboratories (alloys in bridges, crowns etc.)	Cleaners or rebuilders of furnaces where beryllium was present/used
Bicycle and golf club manufacturing	
Plastics injection molding	
Beryllium mining and processing	

b. Outcome: a medical condition that meets the diagnostic criteria in this Guideline.

c. Relationship: generally accepted scientific evidence, which establishes on a more probable than not basis (greater than 50%) that the workplace activity (exposure) in an individual case was a proximate cause of the development or worsening of the condition (outcome).

Currently accepted scientific evidence provides that "Chronic beryllium disease [is]…caused by exposure to beryllium." [12] Also, "CBD only develops in workers who have become sensitized to beryllium," which may occur "at any point during job exposure, or in some cases [workers] may not become sensitized until after leaving a job where there has been beryllium exposure."[3]

The amount or duration of exposure needed to develop sensitization is not known, but there is evidence that even minimal or brief beryllium exposures can lead to beryllium sensitization and CBD. [2, 6] There is evidence that the OSHA 2.0 $\mu g/m^3$ standard does not protect against developing CBD, [2, 13] and medical literature states "it is not possible to identify an occupational exposure limit that will prevent all cases of CBD".[13] The prevalence of sensitization to beryllium has been observed to vary by industry and job or process type.[6] Although studies of exposure-response are inconsistent, there is evidence of association between increased exposure to beryllium and developing CBD.[2]

Medical literature shows beryllium exposure may be unrecognized,[2] and demonstrates, for example, that CBD misdiagnosed as sarcoidosis has been identified by taking a work history and using the BeLPT.[10] For these reasons, Labor and Industries recommends clinicians obtain a work history and consider referral to a center for chemically-related illness when an exposure assessment has not been performed, or if evaluation of unexpected evidence of beryllium sensitization is required. Contact L&I Office of the Medical Director for referral assistance.

BERYLLIUM SENSITIZATION

Sensitization to beryllium is an immunologic response at a cellular level and is dependent on host factors and exposure factors. Host factors refer to a genetic susceptibility for having immune-mediated response to beryllium. Genetic testing is not a suitable screening test because the prevalence of the genetic susceptibility is high in the general population. [12]

The standard test for beryllium sensitization is the beryllium lymphocyte proliferation test (BeLPT), which can be performed on either a blood sample or fluid obtained via bronchoalveolar lavage (BAL). Before the BeLPT was available, a skin patch test was used, but this test is not recommended by Labor and Industries (L&I) because the test itself can induce beryllium sensitization in previously un-sensitized individuals.[2, 7] The bronchoalveolar lavage LPT is considered especially useful diagnostically when evaluating for CBD in the setting of negative blood LPTs, though cigarette smoking and immunosuppressants can cause false negative results in BeLPT tests obtained from BAL. [2, 12]

To confirm beryllium sensitization, L&I requires one of the following criteria be met (these tests could have been performed at any time after the exposure):

1. At least two abnormal blood BeLPT tests* [2] OR
2. At least one abnormal and one borderline blood BeLPT tests* [2] OR
3. At least three borderline blood BeLPT tests*† [2, 14] OR
4. An abnormal bronchoalveolar lavage BeLPT if performed [2] OR
5. Positive skin patch test to beryllium if performed [2]. Labor and Industries does not recommend skin patch testing to diagnose chronic beryllium disease due to the risk of inducing sensitization. [2, 7]

* Obtaining at least two tests improves the accuracy of test results.[14-16] Blood BeLPT testing algorithms obtain higher sensitivity by splitting the initial blood sample between two laboratories, while keeping the risk of a false positive low. [15] Labor and Industries therefore recommends splitting the initial peripheral blood sample when performing BeLPT testing in circumstances where ongoing serial testing is not assured. [15]

† Middleton et al determined that the predictive value of three borderline results was higher than the minimum three result combination that meets criterion 2 b (1 abnormal + 1 borderline + 1 normal LPT). [14]

CHRONIC BERYLLIUM DISEASE

Chronic beryllium disease (CBD) is a granulomatous disease that most often manifests in the lungs; it rarely affects other organs.[1, 7] Certain extrapulmonary manifestations are considered primarily historical.[2, 10] The period between the first beryllium exposure and the onset of CBD ranges from months to decades.[10, 17, 18]

Because the symptoms of CBD are mostly respiratory in nature, it can be confused with other possible diagnoses such as sarcoidosis, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, asthma, and other granulomatous lung diseases. [12, 19]

The two diagnostic pathways L&I uses to confirm CBD follows that of the current Official American Thoracic Society (ATS) Statement: Diagnosis and Management of Beryllium Sensitivity and Chronic Beryllium Disease.[2] The characteristics of the BeLPT indicate most patients with chronic beryllium disease can be diagnosed using this test as described in the primary diagnostic pathway.[14, 15, 20] However, the primary diagnostic pathway may not be sufficient for some patients because the sensitivity of the blood BeLPT is not 100%,[20] and the BAL BeLPT can be falsely negative, for instance in cigarette smokers [19] or patients taking immunosuppressive medication. [2]

Diagnosing CBD requires:

Primary Diagnostic Pathway:

1. Evidence of beryllium sensitization as defined above, AND
2. EITHER:
    a. Lung biopsy showing granulomatous inflammation (typically noncaseating granulomas), OR
    b. Clinical presentation and diagnostic findings consistent with CBD, such as from imaging studies, or bronchoalveolar lavage.

Secondary Diagnostic Pathway: [Due to the medical complexities associated with the condition and the application of these four criteria Labor and Industries requires face-to-face evaluation be performed by a board certified occupational medicine physician (to assess exposure) AND a board certified pulmonologist (to assess clinical presentation)]

3. If both blood BeLPT and bronchoalveolar lavage BeLPT (unless medically contraindicated) as described above do not confirm sensitization, AND all four of the following are met:
    a. Known scientific or medical basis for the false negative blood and BAL BeLPT results, AND
    b. The patient has a clinical presentation and objective findings consistent with CBD, e.g. a lung biopsy confirming the presence of granulomas that are consistent with CBD, or a past positive BeLPT, AND
    c. Other causes of granulomatous lung disease have been excluded, such as mycobacterial and fungal infection; hypersensitivity pneumonitis; and sarcoidosis,[§] AND
    d. There is strong evidence of exposure to beryllium, e.g. through a documented occupational injury, exposure monitoring demonstrating exposure, or confirmed cases of beryllium sensitization in individuals known to have experienced similar exposures to the patient.

[§] While there are multiple clinical similarities between chronic beryllium disease and sarcoidosis, they are distinct conditions. For example, the following disease manifestations occur with sarcoidosis but not with chronic beryllium disease: erythema nodosum; lupus pernio; involvement of the central nervous system, peripheral nervous system, or eye (except acute conjunctivitis).[2, 10]

CLINICAL SYMPTOMS OF CBD

Clinical evaluation and diagnosis of someone with possible chronic beryllium disease requires obtaining a careful history and physical that considers prior exposure to beryllium as well as the signs, symptoms, and tests for CBD that are highlighted in Table 2.

Table 2. Signs, symptoms and test results of CBD [8, 12, 21]

Per History and Physical

- Non-productive cough
- Abnormal lung sounds (crackles)
- Chest discomfort
- Dyspnea on exertion
- Fever
- Weight loss
- Night sweats
- Fatigue
- Loss of appetite

Per Tests and Procedures

- Chest x-ray or CT scans show small lung scars, hilar adenopathy (enlargement of lymph nodes in the central part of the chest), and/or most commonly reticular-nodular infiltrates
- Abnormal results from pulmonary function tests, such as restrictive, obstructive, or mixed patterns, or showing reduced carbon monoxide diffusing capacity
- Hypoxemia by arterial blood gases or oximetry, and oxygen desaturation with exercise
- Granulomas found in lung or skin tissue per biopsy
- Lymphocytosis on bronchoalveolar lavage

FOLLOW-UP FOR BERYLLIUM SENSITIZED WORKERS

Chronic beryllium disease can be present without obvious symptoms, and the latency between exposure and manifestation of disease ranges from months to decades.[10, 17, 18] Because of this long latency, workers might file an initial claim years after a work-related exposure, or might need to re-open a claim filed years before, to receive care for their beryllium-related condition.

Workers with beryllium sensitization require periodic medical evaluation (see Table 3) to monitor for progression to chronic beryllium disease, at least every 2-3 years, and more frequently if clinical concern requires.[2, 22] Patients with known chronic beryllium disease are usually evaluated more frequently, e.g. at least annually or more often according to clinical need.[2, 23]

Table 3. Recommended frequency of medical evaluation among workers with known sensitization or CBD

Beryllium sensitization	**Chronic beryllium disease**
At least every 2-3 years	At least annually

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