Agency for Toxic Substances and Disease Registry (ATSDR)
Case Studies in Environmental Medicine
Beryllium Toxicity

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Table of Contents

Key Concepts	• Beryllium produces health effects ranging from sensitization without evidence of disease to clinically apparent pulmonary disease. • Chronic beryllium disease may be misdiagnosed as sarcoidosis. • Immunologic tests can detect beryllium sensitization and help clinicians differentiate between chronic beryllium disease and other interstitial lung diseases.
About This and Other Case Studies in Environmental Medicine	This educational case study document is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to promote the adoption of medical practices that aid in the evaluation and care of potentially exposed patients. The complete series of *Case Studies in Environmental Medicine* is located on the ATSDR Web site at URL: www.atsdr.cdc.gov/csem/. In addition, the downloadable PDF version of this educational series and other environmental medicine materials provides content in an electronic, printable format, especially for those who may lack adequate Internet service.

How to Apply for and Receive Continuing Education Credit	See Internet address www2.cdc.gov/atsdrce/ for more information about continuing medical education credits, continuing nursing education credits, and other continuing education units.
Acknowledgements	We gratefully acknowledge the work that the medical writers, editors, and reviewers have provided to produce this educational resource. Listed below are those who have contributed to development of this version of the *Case Study in Environmental Medicine*. **ATSDR Authors:** Kim Gehle, MD, MPH **CDC/ATSDR Planners:** Valerie J. Curry, MS; John Doyle, MPA; Bruce J. Fowler, Ph.D.; Kimberly Gehle, MD; Sharon L. Hall, Ph.D.; Michael Hatcher, DrPH; Kimberly Jenkins, BA; Ronald T. Jolly; Delene Roberts, MSA; Oscar Tarrago, MD, MPH, CHES; Brian Tencza, MS; Pamela Tucker, MD **CDC/ATSDR Commenters:** Dan Middleton, MD, **Contributors:** Robert Johnson MD **Peer Reviewers:** Lisa A. Maier, MD, FCCP, MSPH, ; Lisa Barker, Peggy Mroz
Disclaimer	The state of knowledge regarding the treatment of patients potentially exposed to hazardous substances in the environment is constantly evolving and is often uncertain. In this educational monograph, ATSDR has made diligent effort to ensure the accuracy and currency of the information presented, but makes no claim that the document comprehensively addresses all possible situations related to this substance. This monograph is intended as an educational resource for physicians and other health professionals in assessing the condition and managing the treatment of patients potentially exposed to hazardous substances. It is not, however, a substitute for the professional judgment of a health care provider. The document must be interpreted in light of specific information regarding the patient and in conjunction with other sources of authority. Use of trade names and commercial sources is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry or the U.S. Department of Health and Human Services.
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How to Use This Course

Introduction	The goal of Case Studies in Environmental Medicine (CSEM) is to increase the primary care provider's knowledge of hazardous substances in the environment and to help in evaluation and treating of potentially exposed patients. This CSEM focuses on beryllium toxicity.
Available Versions	Two versions of the Beryllium Toxicity CSEM are available. • The online version (http://www.atsdr.cdc.gov/csem/beryllium/) provides the content through the Internet. • The downloadable PDF version provides content in an electronic, printable format, especially for those who may lack adequate Internet service. The HTML version offers interactive exercises and prescriptive feedback to the user.
Instructions	To make the most effective use of this course: • Take the Initial Check to assess your current knowledge about beryllium toxicity. • Read the title, learning objectives, text, and key points in each section. • Complete the progress check exercises at the end of each section and check your answers. • Complete and submit your assessment and posttest response online if you wish to obtain continuing education credit. Continuing education certificates can be printed immediately upon completion.
Instructional Format	This course is designed to help you learn efficiently. Topics are clearly labeled so that you can skip sections or quickly scan sections you are already familiar with. This labeling will also allow you to use this training material as a handy reference. To help you identify and absorb important content quickly, each section is structured as follows:

Section Element	Purpose
Title	Serves as a "focus question" that you should be able to answer after completing the section
Learning Objectives	Describes specific content addressed in each section and focuses your attention on important points
Text	Provides the information you need to answer the focus question(s) and achieve the learning objectives
Key Points	Highlights important issues and helps you review
Progress Check	Enables you to test yourself to determine whether you have mastered the learning objectives
Answers	Provide feedback to ensure you understand the content and can locate information in the text

Learning Objectives	Upon completion of the Beryllium Toxicity CSEM, you should be able to

Content Area	**Objectives**
Exposure Pathways	• Describe beryllium's properties. • Describe how people are exposed to beryllium.
Standards and Regulations	• Describe the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for beryllium. • Describe the U.S. Environmental Protection Agency (EPA) regulation for beryllium emissions in air .
Populations at Risk	• Identify the populations most heavily exposed to beryllium. • Identify who is at risk of exposure to beryllium in the home. • Name a marker of genetic susceptibility to beryllium exposure.
Health Effects	• Describe two mechanisms of injury resulting from beryllium exposure. • Describe the health conditions associated with beryllium exposure.
Clinical Assessment	• Describe chest radiograph findings associated with beryllium-related diseases. • Describe pulmonary function test findings associated with beryllium-related diseases. • Identify other tests that can assist with diagnosis of beryllium-related diseases.
Treatment and Management	• Identify what patients should be treated . • Identify the primary drug for treatment of chronic beryllium disease (CBD). • Describe possible sequelae of chronic beryllium disease.

Initial Check

Instructions	This Initial Check will help you assess your current knowledge about beryllium toxicity. Read the case study below, and then answer the questions that follow.
Case Study	***A 14-year-old daughter of a dental technician has a cough, is wheezing, and has a low-grade fever.*** The patient has developed a troublesome cough and sometimes at night cannot catch her breath. Her cough has recently worsened, with an increase in sputum production and chest discomfort. Last night she had a particularly rough time, but she had no wheezing or fever. Chart review reveals no known history of asthma or allergies. The patient's height and weight are appropriate for her age. Her two siblings, aged 6 and 12 years, are in good health. History of previous illness reveals three episodes of otitis media as a young child, but no other significant illness. She has no history of eczema or food intolerance. In response to your questions, the mother tells you that her husband, a dental technician, has been diagnosed with sarcoidosis. He recently had flu-like symptoms similar to those of his daughter, including fatigue, nasal congestion, sneezing, and cough. Although her husband, who smokes cigarettes, has had a cough for several years, the mother states that her daughter developed symptoms a few days after her husband's latest bout. She wonders if her husband's sarcoidosis could have been transmitted to their daughter. Examination reveals a cheerful girl in no acute distress. Her temperature today is 100ºF, respiratory rate is 24 breaths per minute, without retractions or audible wheezing, and her pulse is 90 beats per minute and regular. Significant findings include a mildly inflamed pharynx and anterior cervical lymph nodes that are slightly enlarged and mildly tender. Tympanic membranes are clear. Auscultation of the lungs reveals mild and diffuse expiratory wheezing with occasional rhonchi. Results of cardiac and abdominal examinations are normal. Chest radiograph shows minimal peribronchial thickening, but it is otherwise normal.
Initial Check Questions	1. Construct a problem list and a differential diagnosis for the daughter. 2. What further questions might you ask about the father? 3. What is the most likely diagnosis for the daughter? 4. Could the father pass beryllium to other family members by contact or by coughing or sneezing? 5. What organ systems should be evaluated if beryllium exposure is suspected? 6. What steps would you take to evaluate the condition of the daughter in the case study? 7. What steps will be necessary to evaluate her father's condition? 8. The father's blood beryllium lymphocyte proliferation test (BeLPT) test was abnormal. It was repeated and was again abnormal, consistent with beryllium sensitization. What is appropriate treatment of the father's condition?

Initial Check Answers

1. The patient's problem list includes productive cough, wheeze, and low-grade fever. The most likely causes to consider for this patient's condition are reactive airway disease, asthma, an infectious process (viral or bacterial bronchitis, sinusitis, or pneumonia), and chemical irritation (cigarette smoke or air pollution). Considerations in younger patients might also include bronchiectasis, congenital abnormalities, foreign-body aspiration, and cystic fibrosis.

   The information for this answer comes from section "How Should Patients Exposed to Beryllium Be Evaluated?"

2. Initially, you would want to know the father's general state of health, his full work history, smoking habits, and history of respiratory problems. You may also wish to explore his hobbies and home environment. As a dental laboratory technician, the father may be at risk of exposure to beryllium (during casting and grinding of alloys used in dental prostheses), as well as to mercury (during mixing of dental amalgams). Chronic cough is a common symptom of chronic beryllium disease, which can be misdiagnosed as sarcoidosis unless an immunological test specific to beryllium sensitization is used.

   The information for this answer comes from section "How Should Patients Exposed to Beryllium Be Evaluated?"

3. Asthma or bronchitis would both be high on your list. Wheezing, if present, could be a complication of bronchitis, or it could be a new onset of asthma triggered by infection or exacerbated by smoke from her father's cigarettes. Workers who cast or grind beryllium can bring the dust home on their hair, skin, and clothes, from which members of their households may be exposed. Such exposed household members have developed chronic beryllium disease. Based on her acute signs and symptoms, it is unlikely that the patient has a beryllium-related disease. However, if she visits her father's workplace, or if he does not change work clothes before leaving the workplace, she should be considered at risk.

   The information for this answer comes from section "How Should Patients Exposed to Beryllium Be Evaluated?"

4. No evidence suggests that beryllium sensitization or disease can be passed on by body fluids, coughing, or sneezing. However, beryllium exposure of family members can occur via contaminated clothes. To ensure that beryllium is not brought home from the workplace through beryllium-contaminated clothes and skin, you should discuss with the father proper workplace hygiene, including changing clothes and showering before leaving the workplace.

   The information for this answer comes from section "Who Is At Risk of Beryllium Exposure?"

5. Chronic beryllium disease manifests mainly in the lungs as a granulomatous interstitial pneumonitis. The skin should also be evaluated because beryllium can lead to dermatitis, ulceration, granuloma formation, and poor wound healing.

   The information for this answer comes from section "What Other Tests Can Assist With Diagnosis of Beryllium-Related Disease?"

6. For the daughter, initial evaluation should include a careful history, thorough physical examination, and a chest radiograph. The history suggests the presence of an infectious process or asthma. Screening blood work or peak flow rates might be considered at this time, depending on the severity of symptoms. If her respiratory symptoms become chronic, she should be re-evaluated and possibly referred to a specialist. A blood BeLPT might be considered if you highly suspect beryllium exposure.

   The information for this answer comes from section "How Should Patients Exposed to Beryllium Be Evaluated?"

7. Due to proven beryllium exposure, the father is a candidate for a more complete evaluation for beryllium toxicity. Referral to a pulmonologist familiar with the workup of chronic beryllium disease would be appropriate at this time. An abnormal BeLPT would indicate a good likelihood that his pulmonary abnormalities are due to beryllium exposure.

   The information for this answer comes from section "How Should Patients Exposed to Beryllium Be Evaluated?"

8. The father has beryllium sensitization based on two abnormal blood Beryllium Lymphocyte Proliferation Tests. The first therapeutic effort should be to remove him from further exposure to beryllium. Another important step for symptom relief may be to help the patient stop smoking.

   Bronchoscopy with bronchoalveolar lavage and biopsy may be performed by the pulmonologists to establish a diagnosis of chronic beryllium disease. The following baseline tests are often performed:

   - chest radiograph,
   - pulmonary function tests,
   - carbon monoxide diffusion, and
   - exercise physiology with arterial blood gases.

   The patient's health should be followed on a regular basis to monitor declines in physiology and development of symptoms.

   If appropriate, corticosteroid therapy may be instituted by the pulmonary physician managing this patient. The father should be re-evaluated periodically to assess his response to corticosteroids, and

to taper the dose to the minimum needed to control symptoms and maintain physiologic improvement. He should also be monitored for potential long-term steroid side effects.

Because the father may represent a sentinel case, the local health department should be notified. To prevent further exposures, the patient's workplace should be evaluated. Notification of the Occupational Safety and Health Administration or a patient request for a National Institute for Occupational Safety and Health (NIOSH) health hazard evaluation may be warranted.

The information for this answer comes from section "How Should Patients Exposed to Beryllium Be Treated?"

What Is Beryllium and How Are People Exposed To It?

Learning Objective	Upon completion of this section, you will be able to • describe beryllium's properties, and • describe how people are exposed to beryllium.
What Is Beryllium?	Pure beryllium, one of the lightest metals known, is a hard, grayish material obtained from the minerals bertrandite and beryl. Gem-quality beryl is known as either aquamarine or emerald. Beryllium has unique properties such as strength, electrical and thermal conductivity, and resistance to corrosion (Stonehouse and Zenczak 1991) which makes the use of the metal and its oxide attractive in a wide range of technological applications (Weston *et al.* 2005). Although beryllium is a naturally occurring substance, the major source of its emission into the environment is the combustion of fossil fuels (primarily coal), which releases beryllium-containing particulates and fly ash into the atmosphere. Beryllium is relatively water insoluble and adsorbs tightly to soil therefore, it is not often a drinking water contaminant. It has been found in various foodstuffs, but bioaccumulation in the food chain is not significant (Taylor *et al.* 2003; Kolanz *et al.* 2001).
How Are People Exposed to Beryllium?	Most exposures to beryllium that cause disease are related to some aspect of beryllium processing. Because of its unique properties, beryllium is used in many high-technology consumer and commercial products. The major pathway for human exposure is through airborne particles of beryllium metal, alloys, oxides, and ceramics (Kolanz 2001). Beryllium particles are inhaled into the lungs and upper respiratory tract. Exposures not directly related to inhalation of workplace air, such as hand-to-mouth exposure, dermal contact with ultrafine particles, and resuspension following deposition of beryllium dust onto clothing may also occur (Kolanz *et al.* 2001; Deubner *et al.* 2001; Tinkle *et al.* 2003).
Key Points	• Some individuals exposed to beryllium develop sensitization and are at risk of developing chronic beryllium disease (CBD). • CBD is primarily an occupational lung disease, but it has been reported in household contacts of beryllium workers and individuals living near beryllium facilities.

Progress Check

1. The following are true regarding beryllium except

   A. Beryllium is one of the heaviest metals known.
   B. Pure beryllium is a naturally occurring hard, grayish material obtained from the mineral rocks bertrandite and beryl.
   C. The major source of its emission into the environment is combustion of fossil fuels.
   D. Beryllium is relatively water insoluble and adsorbs tightly to soils.

To review relevant content, see "What Is Beryllium?" in this section.

2. The major pathway for beryllium exposure is

   A. eating contaminated food
   B. inhaling airborne particles
   C. drinking tap water
   D. using a microwave oven.

To review relevant content, see "How Are People Exposed to Beryllium?" in this section.

What Are the Standards and Regulations for Beryllium Exposure?

Learning Objective

Upon completion of this section, you will be able to

- describe the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for beryllium, and
- describe the U.S. Environmental Protection Agency (EPA) regulation for beryllium emissions in air.

Introduction

Table 1 shows standards and regulations for beryllium. The occupational exposure limit of 2.0 micrograms per cubic meter (µg /m^3) of air for an 8-hour work shift for beryllium has been used in the workplace since the late 1940s. However, recent research has shown that the 2.0 µg/m^3 standard is not protective (For example, see the ACGIH standards). Ongoing and planned research is anticipated to support the development of one or more scientifically sound standards for the different chemical forms of beryllium (Paustenbach *et al.* 2001). The health data currently available support further reductions in exposure levels to help minimize the incidence of chronic beryllium disease (Wambach and Tuggle 2000). Additional international, national, and state regulations and guidelines regarding beryllium in air, water, and other media are summarized in Table 8-1 of the 2002 ATSDR Toxicological Profile on Beryllium (www.atsdr.cdc.gov/toxprofiles/tp4.html).

Workplace Standards

Air

The OSHA regulation for beryllium and its compounds is an 8-hour time-weighted average (TWA) of 2 micrograms (as beryllium) per cubic meter of air (2 µg/m^3).

An employee should not be exposed to a concentration of beryllium and beryllium compounds exceeding 5 µg/m^3.

The 30-minute maximum peak level is 25 µg/m^3.

NIOSH recommends that beryllium be treated as a potential human carcinogen and advises a 10-hour TWA not to exceed 0.5 µg/m^3.

Environmental Standards

Air

Beryllium has been designated a hazardous air pollutant under the Clean Air Act. According to EPA regulations, beryllium emissions from stationary sources cannot exceed 10 g (0.022 lbs) over a 24-hour period.

Ambient air concentrations averaged over a 30-day period near stationary sources must not exceed 0.01 µg/m^3.

Water

The EPA advisory for beryllium in water is less than 68 nanograms per liter (ng/L) for consumption of 2 L of ambient water per day.

Table 1. Standards and Regulations for Beryllium

Agency	Focus	Level	Comments
American Conference of Governmental Industrial Hygienists	Air: workplace	2 µg/m^3 0.05 µg/m^3 0.2 µg/m^3	Advisory; TLV-TWA* Notice of Intended Change, 2007; TLV-TWA* Notice of Intended Change, 2007: STEL‡
National Institute for Occupational Safety and Health (NIOSH)	Air: workplace	0.5 µg/m^3	Advisory; 10-hour TWA; REL**
Occupational Safety and Health Administration (OSHA)	Air: workplace	2 µg/m^3 5 µg/m^3 25 µg/m^3	Regulation; PEL† as TWA Regulation; Ceiling Regulation; STEL‡ 30-minute maximum peak
U.S. Environmental Protection Agency (EPA)	Air emissions	10 g/24 hours	Regulation

* TLV-TWA (threshold limit value-time-weighted average): time-weighted average concentration to which nearly all workers may be repeatedly exposed for a normal workday and a 40-hour workweek.

† PEL (permissible exposure limit): highest level of beryllium in air to which a worker may be exposed, averaged over an 8-hour workday.

**REL (recommended exposure limit): TWA indicates a time-weighted average concentration for up to a 10-hour workday during a 40-hour workweek.

‡ STEL (short-term exposure limit): usually determined by a 15-minute sampling period.

µg/m^3 = micrograms per cubic meter; g = grams

Key Points

- OSHA's current 8-hour TWA for beryllium is 2 µg/m^3. Research shows that this level may not be protective.
- The EPA regulation for beryllium emissions in air is 10 g in a 24-hour period.

Progress Check

3. It is a federal (OSHA) regulation that workers not be exposed to more than 2 µg/m^3 of beryllium in air

   A. Averaged over an 8-hour workday.
   B. At any time during the day.
   C. If they have underlying lung disease.
   D. If they are not wearing a paper dust mask.

   To review relevant content, see "Standards and Regulations for Beryllium" in this section.

4. The OSHA regulation of 2 µg/m^3 is

   A. Relatively new.
   B. Not meant to be strictly enforced.
   C. Lower than the NIOSH advisory level.
   D. Unchanged since the 1940s and may not be protective.

   To review relevant content, see "Introduction" in this section.

5. The EPA regulation for beryllium emissions in air is

   A. 10 µg in a 24-hour period.
   B. 10 g in a 24-hour period.
   C. 10 g averaged over an 8-hour workday.
   D. 10 µg averaged over an 8-hour workday.

   To review relevant content, see "Environmental Standards" and Table 1 in this section.

Who Is at Risk of Exposure to Beryllium?

Learning Objectives	Upon completion of this section, you will able to • identify the populations most heavily exposed to beryllium, and • identify who is at risk of exposure to beryllium in the home.
Overview of Risk of Exposure	Beryllium disease was first noted in the 1930s in Europe. In the 1940s, reports of disease related to beryllium surfaced among workers exposed to beryllium-containing phosphors in the fluorescent lamp industry and the nuclear weapons industry (Kress and Crispell 1944). Industry standards and environmental controls for beryllium were initially established in the late 1940s. At least 134,000 current U.S. workers are estimated to be exposed to beryllium, though precise numbers for the total number of workers exposed to beryllium are unavailable (Henneberger *et al.* 2004). This count does not include former workers, contract workers, and construction workers exposed in beryllium using facilities. Outside the United States, more and more industries are being identified with current or former beryllium exposure (Newman *et al.* 2005; Glazer and Newman 2003).
Occupational Exposure	Risk to workers depends considerably on their work tasks. For example, machinists in both ceramics and nuclear weapons manufacture have been found to have an increased risk of developing sensitization. This is probably due to small respirable particles of beryllium (<10 microns) that may be better able to deposit deep in the lungs. Other studies have shown that laboratory workers and construction workers in beryllium-using facilities are also at increased risk. However, numerous individuals with apparently trivial exposure, such as security guards, secretaries, and bystanders, have also developed disease. This suggests that a linear dose response may be absent. Inhaling metallic beryllium, beryllium oxide, beryllium-copper and other alloys, or beryllium salts are the major exposure risks leading to disease (Martyny *et al.* 2000; Sawyer *et al.* 2002; Willis and Florig 2002).
In What Industries Might Workers Be Exposed to Beryllium?	Industries and occupations with potential beryllium exposure include • aerospace, • automotive parts, • computers, • construction trades, • dental supplies and prosthesis manufacture, • electronics, • industrial ceramics, • laboratory workers, • metal recycling, • mining of beryl ore (beryl ore extraction), • nuclear weapons, • precision machine shops, • smelting/foundry, • tool and die manufacture, and • welding.

Beryllium Sensitization	Beryllium sensitization (BeS) is found in 1% - 16% of exposed workers tested with the blood Beryllium Lymphocyte Proliferation Test (Saltini *et al.* 2001; Henneberger *et al.* 2001). Individuals may have BeS without disease, which is not associated with any symptoms or clinical abnormalities in pulmonary function tests or chest radiography. These individuals have a risk of developing chronic beryllium disease (CBD) in the future at a rate of 6% to 8% per year (Newman *et al.* 2005). In addition to total beryllium mass, factors such as chemical composition, particle size, number, and surface area may influence bioavailability of beryllium and contribute to risk of sensitization and disease (Henneberger *et al.* 2001; Stefaniak *et al.* 2004; Deubner *et al.* 2001).
Chronic Beryllium Disease (CBD)	CBD is typically considered only when there is known work exposure; however, CBD has also occurred in occupational and environmental settings where exposure was unexpected (Middleton 1998). Many individuals have developed BeS and CBD working in areas where air concentrations are found to be below the recommended workplace exposure limits (Maier 2001). Sensitization and disease has been reported in security guards, secretaries, and custodial staff who work at facilities using beryllium (Frome *et al.* 2003). CBD due to secondary contamination has been caused by exposure to beryllium from a workers' clothing (Newman and Kreiss 1992). BeS and CBD have been diagnosed among individuals living near beryllium-using facilities from which they received high exposures in the past.
Key Points	• Anyone working with or around beryllium metal, ceramics, alloys, or salts is at risk of developing beryllium sensitization or disease from inhaling small particles. • Very low concentrations of beryllium in air can cause sensitization and disease. • People living near a plant that uses beryllium and families of workers have developed CBD.
Progress Check	6. Of the following, who is likely to be at risk of beryllium exposure? A. Dental supplies and prosthetics worker. B. Industrial ceramics fabricator. C. Machinist in the aerospace industry. D. All of the above. *To review relevant content, see "In What Industries Might Workers Be Exposed to Beryllium?" in this section.* 7. Important factors determining sensitization to beryllium containing particles after exposure may include A. Total mass of particles. B. Size and number of particles. C. Particle surface area. D. All of the above. *To review relevant content, see "Beryllium Sensitization" in this section.*

8. A worker's family members may be exposed to beryllium by

   A. Sharing utensils with the worker.
   B. Kissing the worker.
   C. Gathering and washing the worker's dirty clothes.
   D. Living beneath high-voltage power lines.

To review relevant content, see "How Are People Exposed to Beryllium" in the previous section and "Chronic Beryllium Disease (CBD)" in this section.

Who Is Susceptible to Beryllium Exposure?

Learning Objective	Upon completion of this section, you will be able to • name a marker of genetic susceptibility to beryllium exposure.
Overview of Susceptibility	Beryllium sensitization (BeS) is found in a wide range of exposed workers (1%–16%) in beryllium-related industry (Saltini *et al.* 2001). Individual susceptibility to sensitization and exposure circumstances are both important in developing chronic beryllium disease (CBD) (Kreiss *et al.* 1993). In CBD, a susceptible person develops a cell-mediated, delayed hypersensitivity reaction after beryllium exposure (Tinkle *et al.* 1999). This hypersensitivity leads to a spectrum of immune abnormalities and the eventual pathological changes of CBD (Dotti *et al.* 2004).
The Genetics of Beryllium Sensitization and Disease	Specific genes have been identified as candidates that convey increased risk of BeS and/or CBD in persons exposed to beryllium (Richeldi *et al.* 1993; Richeldi *et al.* 1997; Wang *et al.* 1999; Wang *et al.* 2001; Saltini *et al.* 2001; Rossman *et al.* 2002; Maier *et al.* 2003; McCanlies *et al.* 2004; McCanlies *et al.* 2003; Weston *et al.* 2005; McCanlies *et al.* 2007; Dotti *et al.* 2004; Sato *et al.* 2007). The strongest association has been found with a human leukocyte antigen gene (*HLA-DPβ1*), but this is complicated because this gene has more than 120 variants. The easiest concept is that variants coding for a glutamate (glutamic acid, also known as a supratypic marker) in the 69th position (Glu69) are at high risk, between 2 and 20 fold (McCanlies *et al.* 2003; Weston *et al.* 2005). However, the exact genetic risk level is not known because too few cases have been studied and other factors, exposure levels (gene environment interactions) and genes not yet studied in CBD (*e.g.*, cytokines), may be involved. Thus, further efforts are needed to explore these factors (Richeldi *et al.* 1997; Weston *et al.* 2005). Current wisdom is that *HLA-DPβ1* variants that are Glu69 positive each present a different degree of risk for BeS and CBD in persons exposed to beryllium. In the case of the Tumor Necrosis Factor-alpha gene (*TNF-α*) a number of studies have been performed, but no clear result has emerged. *TNF-α* is a pro-inflammatory cytokine that when stimulated, results in inflammation. It has been implicated in arthritis and other immunological dysfunctional conditions. Since CBD has an inflammatory component, *TNF-α* is a logical candidate CBD susceptibility gene. Again, based on current knowledge a more rigorous study design needs to be developed and implemented before this gene can be implicated in or eliminated from the list of genetic risk factors for BeS and CBD in persons exposed to beryllium (Saltini *et al.* 2001; McCanlies *et al.* 2007; Dotti *et al.* 2004; Sato *et al.* 2007).
Key Points	• In BeS and CBD, a susceptible person develops a cell-mediated, delayed hypersensitivity reaction after beryllium exposure. • Both individual susceptibility and exposure circumstances are important in developing CBD.

Progress Check

9. The *HLA-DPβ1* genes with the supratypic marker Glu69 may lead to an increased risk to those exposed to beryllium by as much as

   A. 2-fold
   B. 20-fold
   C. 2-20-fold
   D. No increased risk.

To review relevant content, see "The Genetics of Beryllium Sensitization and Disease" in this section.

10. Genetic susceptibility screening is uniformly performed in the beryllium industry.

    A. True.
    B. False.

To review relevant content, see "The Genetics of Beryllium Sensitization and Disease" in this section.

How Does Beryllium Induce Pathogenic Changes?

Learning Objective	Upon completion of this section, you will be able to • describe two mechanisms of injury resulting from beryllium exposure, and • describe the health conditions associated with beryllium exposure.
Acute *versus* Chronic Disease	Two distinct mechanisms of injury can result from beryllium exposure. In acute disease, high levels of beryllium exposure can result in inflammation of the upper and lower respiratory tract and airways, bronchiolitis, pulmonary edema, and chemical pneumonitis. (Kim 2004). Acute beryllium disease occurs less commonly than chronic beryllium disease (CBD). CBD, sometimes called berylliosis, is primarily a pulmonary disorder in which granulomatous inflammation develops after exposure and subsequent sensitization to beryllium. The lungs and thoracic lymph nodes are the primary sites involved. In addition, beryllium exposure can cause skin disease. Rarely, CBD can involve the liver, myocardium, salivary glands, and bones (Glazer and Newman 2003). The terms acute and chronic, used to describe beryllium disease, refer to disease processes rather than types of exposure. Acute beryllium disease manifests as an acute chemical pneumonitis, whereas CBD is typically a progressive pulmonary granulomatous lung disease (Sawyer *et al.* 2002). **Table 2** shows possible human health effects of beryllium exposure.

Table 2. Possible human health effects of beryllium exposure (ATSDR, 2002)

Target Organ	Disorder
Respiratory Tract	• Bronchiolitis • Acute pneumonitis • Chronic beryllium disease • Lung cancer • Pulmonary hypertension* • Pneumothorax*
Skin	• Contact dermatitis • Subcutaneous granulomatous nodules • Ulceration • Delayed wound healing
Lymphatic/ Hematologic	• Hilar and mediastinal lymphadenopathy* • Beryllium sensitization

*Occurs in association with chronic beryllium disease.

Respiratory Effects: Acute	Acute beryllium lung disease has been almost completely eliminated in the United States through use of exposure controls. Acute disease manifests as inflammation of the upper or lower respiratory tract or both. The most serious complication is chemical pneumonitis. Acute disease appears suddenly after short exposure to high concentrations or progresses slowly after longer exposure to lower concentrations. Pneumonitis or bronchitis induced by inhaling beryllium is histologically identical to these diseases when caused by other pulmonary irritants (Kress and Crispell 1944).
Respiratory Effects: Chronic	CBD (also known as berylliosis) continues to occur in industries where beryllium and its alloys are processed, smelted, fabricated, and machined—resulting in respirable beryllium particles. CBD is a disorder in which a delayed type IV hypersensitivity response to a persistent antigen (beryllium) leads to noncaseating granuloma formation (Tinkle *et al.* 1999). This interstitial mononuclear cell inflammation and granuloma formation are the primary processes that occur in the lungs and airways of beryllium exposed workers (Sawyer *et al.* 2002). The most common manifestation is chronic interstitial pneumonitis with infiltration of lymphocytes, histiocytes, and plasma cells (Saltini and Amicosante 2001). Beryllium sensitization (BeS) and CBD can occur within 50 days of first exposure in modern industry. Some cases of CBD, however, do not develop until 30 - 40 years after exposure has ceased. On average, CBD usually takes at least 6 - 15 years after exposure to develop into clinically significant respiratory disease (Glazer and Newman 2003; Newman *et al.* 2001).
Dermal Effects	Beryllium-containing particles that lodge in a worker's skin can cause BeS, and lead to ulcerations and delayed wound healing. Biopsy reveals noncaseating granulomas at the site of injury (Berlin *et al.* 2003). Soluble beryllium compounds may cause contact dermatitis. Conjunctivitis, periorbital edema, or upper respiratory tract involvement may occur along with facial contact dermatitis. The use of beryllium-containing dental prostheses can cause the equivalent of oral contact dermatitis and hand lesions in individuals making oral prostheses (Grimaudo 2001).
Carcinogenic Effects	The National Toxicology Program (1999, 2002) lists beryllium and certain beryllium compounds (beryllium-aluminum alloy, beryllium chloride, beryllium fluoride, beryllium hydroxide, beryllium oxide, beryllium phosphate, beryllium sulfate, beryllium zinc silicate, and beryl ore) as substances reasonably anticipated to be carcinogens. The International Agency for Research on Cancer (1993, 2001) has classified beryllium and beryllium compounds in Group 1, carcinogenic to humans, and the U.S. Environmental Protection Agency classifies inhaled beryllium in Group B1, a probably human carcinogen (IRIS 2002). (Sanderson *et al.* 2001, ATSDR 2002). Epidemiological studies have shown an increased risk of lung cancer among beryllium-exposed workers and among workers with acute and CBD. The excess incidence of lung cancer was more pronounced among

	those with acute beryllium disease (SMR = 2.32) than among those with CBD (SMR = 1.57) (Steenland and Ward 1991). Increased lung cancer among workers with higher beryllium exposures and lack of evidence for confounding by cigarette smoking, provide further evidence that beryllium is a human lung carcinogen (Sanderson *et al.* 2001). Some researchers have disputed reported increased risk of lung cancer in beryllium workers in published epidemiologic studies (Levy *et al.* 2002). In addition, mutation and chromosomal aberration assays have yielded somewhat contradictory results. Only a limited number of studies have addressed the underlying mechanisms of the carcinogenicity and mutagenicity of beryllium. It is likely that the different chemical forms of beryllium have different effects on mutagenicity and carcinogenicity, causing some confusion as to mechanisms of carcinogenesis and the cancer risk to humans (Gordon and Bowser 2003).
Key Points	• The most common histology in CBD is granulomatous inflammation on lung biopsy. • Skin contact with beryllium can cause ulceration and subcutaneous granulomas. • Epidemiological studies have shown an increased risk of lung cancer among beryllium-exposed workers and among workers with acute and CBD.
Progress Check	11. The major cause of morbidity and mortality from CBD in the United States is thought to be A. Noncaseating granuloma formation in the lung. B. Coronary artery disease. C. Obesity. D. None of the above. *To review relevant content, see "Respiratory Effects" in this section.* 12. Beryllium is a known human carcinogen. A. True. B. False. *To review relevant content, see "Carcinogenic Effects" in this section.*

Clinical Assessment

Learning Objectives	Upon completion of this section, you will be able to • describe chest radiograph findings associated with beryllium-related diseases, and • identify pulmonary function test findings associated with beryllium-related diseases.
Introduction	The remainder of this case study focuses on a diagnostic approach in chronic beryllium disease (CBD). Although the primary care physician can do the initial visit, history, physical, and basic lab evaluation, positive or suspicious findings warrant referral to a pulmonologist for more definitive evaluation and treatment.
History and Physical Examination	If beryllium exposure is suspected, the respiratory tract and skin should be examined carefully. Initial evaluation of a patient with a history of beryllium exposure should include a thorough occupational and environmental history, medical history, and physical examination. During the medical history and physical examination, particular attention should be focused on the skin and respiratory tract (Rossman 2001; Newman *et al.* 1996).
Signs and Symptoms	Patients with CBD may exhibit a wide spectrum of physical signs and symptoms. Patients with beryllium sensitization (BeS) exhibit no signs or symptoms related to this cell-mediated immune response, except for an abnormal blood beryllium lymphocyte proliferation test (BeLPT). Some patients with CBD identified through workforce medical surveillance with the BeLPT are asymptomatic with only granulomatous inflammation in the lung or an abnormal BeLPT in bronchoalveolar lavage fluid. Patients with CBD may present with a variety of respiratory and systemic symptoms, such as: • nonproductive cough, • fatigue, • exertional dyspnea, • weight loss, • fever, and • myalgias. The earliest clinical signs are scattered bibasilar crackles and wheezing. As the disease progresses, lymphadenopathy may develop, along with cyanosis, digital clubbing, and other signs of chronic lung disease (Glazer and Newman 2003). Beryllium can cause contact dermatitis. If beryllium penetrates the patient's skin or enters open cuts, ulceration or subcutaneous tender nodules can be seen, especially on exposed areas of skin. Cutaneous granulomas can eventually appear. Although rare, cutaneous granulomas can also be a manifestation of the systemic process of CBD, not necessarily related to direct dermal contamination (Berlin *et al.* 2003).

Differential Diagnosis

The differential diagnosis for interstitial and granulomatous lung disease is involved and exhaustive. Conditions that may resemble CBD include

- asbestosis,
- fungal disease,
- hypersensitivity pneumonitis,
- lymphangitic spread of carcinoma,
- pulmonary hemosiderosis,
- sarcoidosis,
- silicosis, and
- tuberculosis (Muller-Quernheim 2005).

Of these, the clinical features of sarcoidosis are most similar to the characteristics of CBD (**Table 3**). Although each disease possesses characteristic clinical features, no feature has proved adequately sensitive and specific to be pathognomonic. CBD does not usually have extrapulmonary manifestations. Furthermore, CBD is progressive and often requires lifelong corticosteroid therapy to slow its course (Glazer and Newman 2003; Fireman *et al.* 2003; Verma *et al.* 2003). Early stage CBD may present similar to asthma with cough, wheezing, shortness of breath, and with obstructive changes on pulmonary function testing.

Table 3. Comparison of clinical features of sarcoidosis and chronic beryllium disease (CBD)

Feature	Sarcoidosis	CBD
Hilar adenopathy	Common	Less common*
Erythema nodosum	Common in acute stage	Absent
Parotid involvement	May be present	Absent
Bone changes	Present in chronic stage	Absent
Response to therapy	Good	Variable†

*About 30% to 40% of patients with CBD exhibit hilar adenopathy.
†CBD is often managed well with corticosteroids, but some patients do not respond to this treatment and experience progressive fibrosis.

Initial Laboratory Evaluation

Initial laboratory evaluation for a patient with a history of beryllium exposure may include: (Glazer and Newman 2003; Newman *et al.* 1996).

- Chest radiograph—often normal, but can reveal diffuse infiltrates and hilar adenopathy if CBD is present. Infiltrates may be nodular or diffusely linear. Hilar adenopathy, noted eventually in 30% to 40% of patients, is usually mild, bilateral, and associated with parenchymal infiltrates.
- Pulmonary function tests—usually normal on initial evaluation but may demonstrate a lower forced vital capacity, and lower diffusion capacity for carbon monoxide. Restriction, obstruction, or a mixed pattern may be evident on pulmonary function tests.
- Arterial blood gas (ABG) can provide an early sign to distinguish beryllium sensitized individuals from those with CBD. Pulse oximetry is not an adequate substitute for ABGs (Lundgren *et al.* 2001). Measures of gas exchange on ABG testing may reveal lower partial pressure of oxygen (PaO_2) at rest, and a higher arterial-alveolar

	gradient at rest if CBD is present (Maier *et al.* 2003). These abnormalities may be more prominent with exercise. • Complete blood count and erythrocyte sedimentation rate (ESR) elevated ESR and hematocrit (due to hypoxemia). • BeLPT.
BeLPT	The BeLPT is an *in vitro* immunologic test that can detect individuals who are sensitized to beryllium and are at risk of progressing to CBD (Stange *et al.* 2004). The BeLPT has revolutionized the approach to the diagnosis, screening, and surveillance of beryllium health effects. The test is based on the development of a beryllium-specific, cell-mediated immune response. The BeLPT has allowed us to define early health effects of beryllium, including BeS, and CBD at an early stage (Maier 2001). This test is performed in only a small number of specialized laboratories. The "Where Can I Find More Information?" section lists some laboratories that perform this test in the United States. Use of trade names and commercial sources is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry or the U.S. Department of Health and Human Services.
How Does the BeLPT Work?	The clinical significance of the BeLPT was described, and a standard protocol developed, in the late 1980s (Frome *et al.* 2003; Kreiss *et al.* 1989). In the BeLPT, a patient's mononuclear cells are collected from blood or bronchoalveolar lavage fluid and then cultured *in vitro* with and without beryllium salts. Cell proliferation is measured by the incorporation of tritiated thymidine in dividing cells. The beryllium-specific cellular immune response is then quantified and reported as a "stimulation index," which is the ratio of the counts per minute of radioactivity in the cells stimulated by beryllium salts divided by the counts per minute for that person's cells that have not been stimulated with any beryllium (Barna *et al.* 2003).
Results	Results may be reported as abnormal, uninterpretable, or negative. Two or more abnormal results constitute possible sensitization of the patient and warrant further work-up by a pulmonologist.
Reliability and Sensitivity	As in other immunologic tests, occasionally results are uninterpretable or may not be perfectly reproducible (Newman 1996). Inter - and intra-laboratory disagreement in results may exist between and within laboratories that conduct this test (Bobka *et al.* 1997; Deubner *et al.* 2001). Nonetheless, the BeLPT is the best available assay and is efficacious in medical surveillance of beryllium-exposed individuals. The sensitivity of the BeLPT is estimated at 68%, with a specificity of nearly 97% (Stange *et al.* 2004). (Confirmation of an abnormal result is recommended to assure appropriate referral for CBD medical evaluation.) The positive predictive value of the BeLPT is comparable to other widely accepted medical tests and is better than other screening tools, including pulmonary function testing, the chest radiograph, and the symptom questionnaire (Glazer and Newman 2003; Stange *et al.* 2004).
Key Points	• CBD is often misdiagnosed as sarcoidosis. • The BeLPT provides a specific test to diagnose BeS and CBD.

Progress Check

13. Initial clinical evaluation for a patient with a history of beryllium exposure might include

    A. Chest radiograph.
    B. Pulmonary function tests.
    C. ABGs.
    D. All of the above.

To review relevant content, see "Initial Laboratory Evaluation" in this section.

14. Possible chest radiograph findings associated with beryllium-related diseases may include

    A. Nodular diffuse infiltrates.
    B. Diffusely linear infiltrates.
    C. Hilar adenopathy.
    D. All of the above.

To review relevant content, see "Initial Laboratory Evaluation" in this section.

15. Possible pulmonary function test findings associated with beryllium-related diseases may include

    A. Lower forced vital capacity and diffusion capacity for carbon monoxide.
    B. Restrictive pattern.
    C. Obstructive pattern.
    D. All of the above.

To review relevant content, see "Initial Laboratory Evaluation" in this section.

16. The BeLPT is an *in vitro* immunologic test that verifies your patient has CBD

    A. True.
    B. False.

To review relevant content, see "BeLPT" in this section.

Clinical Assessment - Other Diagnostic Tests

Learning Objectives

Upon completion of this section, you will be able to

- identify other tests that can assist with diagnosis of beryllium-related diseases.

Bronchoscopy with Lavage and Biopsy

Suspected chronic beryllium disease (CBD) is a clinical indication for bronchoscopy. The bronchoalveolar lavage (BAL) fluid from a patient with CBD typically reveals evidence of lung inflammation, indicated by an elevated white blood cell count with an increased number of lymphocytes. Cells from bronchoalveolar lavage should be tested with the beryllium lymphocyte proliferation test (BeLPT) as previously described in the "Clinical Assessment" section. Lung histopathology reveals interstitial infiltration with mononuclear cells, well-defined noncaseating granulomas (sometimes with multinucleated giant cells and calcific inclusions), and varying degrees of pulmonary fibrosis (Meyer 1994). The granulomas are primarily found in the interstitium and bronchial submucosa.

Other Tests

Besides the BeLPT, several other tests for beryllium sensitization (BeS) or CBD severity have been used, or have been proposed for use. Their ultimate utility is yet to be determined and requires additional research.

- **Patch testing**: Patch testing for BeS has been used in the past. However, beryllium patch testing fell out of favor, in part because of a potential risk of inducing sensitization and a theoretical risk of aggravating underlying disease.
- **Flow cytometric assays (immuno-BeLPT**): T-lymphocyte flow cytometry may provide a sensitive alternative to the traditional BeLPT. It offers a test for sensitization without the use of radioactivity and may prove to be easier to standardize for clinical use (Farris *et al.* 2000; Milovanova *et al.* 2004).
- **Beryllium stimulated serum neopterin**: Neopterin may be a useful diagnostic adjunct in the noninvasive assessment of CBD. Elevated levels differentiate CBD from BeS (Maier *et al.* 2003).
- **ELISPOT analysis**: The frequency of beryllium-specific T cells in the blood of beryllium-exposed subjects is measured using ELISPOT analysis and may be a useful biomarker that helps discriminate between BeS and progression to CBD (Pott *et al.* 2005).

Follow-Up Laboratory Tests

Further laboratory evaluation for a patient with a positive initial workup for CBD is performed to determine disease progression. Additional tests include (Glazer and Newman 2003; Newman *et al.* 1996).

- **Repeat chest radiographs.** The chest radiograph is usually normal in early disease. Later, it may reveal diffuse, bilateral, small opacities predominantly in the middle and upper lung fields, which are similar to the findings in sarcoidosis. The chest radiograph is insensitive for the detection of CBD, so high resolution CT scan (HRCT) may be required. Approximately one third of patients have enlarged hilar or mediastinal lymph nodes. In more advanced cases, honeycombing

may be seen. Importantly, the HRCT may not show evidence of CBD in many cases identified by BeLPT screening (Meyer 1994).

- **Repeat pulmonary function and gas exchange tests.** The most sensitive physiologic test for the detection of CBD is the cardiopulmonary exercise capacity test (Pappas and Newman 1993). The exercise capacity test reveals gas exchange or ventilatory abnormalities, including an elevation in the dead space-to-tidal volume ratio, in most patients with CBD. Exercise test specificity is improved when an indwelling arterial catheter is used (Lundgren *et al.* 2001). For many patients with CBD, results of resting pulmonary function tests, including spirometry values, lung volumes, and carbon monoxide-diffusing capacity (DL_{CO}), are normal but resting and exercise arterial blood gas levels indicate hypoxemia. Most symptomatic patients have resting pulmonary function abnormalities; however, there is no classic pattern, and normal function may be seen. Of those with pulmonary function abnormalities, one third of patients present with an obstructive pattern, one fourth with a restrictive pattern of decreased lung volumes, one third with an isolated decreased DL_{CO}, and the remainder have a mixed pattern of obstruction and restriction with varying amounts of gas exchange abnormality (Newman and Maier 2001). In many patients, disease progresses from an obstructive pattern to a mixed pattern and finally to a purely restrictive pattern as it worsens (Newman 1998).

Overall Approach to the Workup of CBD

Experts in the evaluation and management of suspected CBD have recommended a two-pronged approach:

1. bronchoscopy to establish a definitive diagnosis and,
2. other testing to evaluate the clinical severity.

The clinician must maintain a high degree of suspicion when evaluating any patient who has had direct or indirect beryllium exposure, especially if the patient has respiratory symptoms or diffuse lung disease. It is important not to prejudge the significance of someone's beryllium exposure level, since seemingly trivial exposures may result in disease (Glazer and Newman 2003).

Current diagnostic criteria for CBD require evidence of both BeS and disease (inflammation and granuloma formation) (Newman and Maier 2001). Therefore, once you suspect CBD, the next step is to perform a blood BeLPT. Most clinicians require two positive blood BeLPT results to define sensitization. Patients with positive blood BeLPT results ideally should undergo bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy to look for evidence of pathology, which confirms the diagnosis. In situations where an individual is unable to undergo bronchoscopy for medical reasons, chest radiograph or chest computed tomography (CT) abnormalities consistent with CBD may be used as substitute supporting evidence of granulomatous inflammation. If the clinical suspicion remains high despite negative results on blood BeLPTs, consider referral to a pulmonologist with experience in the diagnosis and

treatment of CBD for further evaluation (Newman 1996).

Many patients identified as sensitized to beryllium have CBD at the time of initial evaluation even if they are asymptomatic and have normal chest radiographs and resting pulmonary function (Henneberger *et al.* 2001). In CBD patients, further testing is warranted, including pulmonary function tests, measurement of DL_{CO}, and exercise capacity testing (preferably with an arterial blood gas analysis) to assess severity of disease. Results from these tests serve as a baseline for future monitoring and as a guide for treatment decisions (Glazer and Newman 2003).

Key Points

- The clinician must maintain a high degree of suspicion when evaluating any patient who has had direct or indirect beryllium exposure, especially if the patient has respiratory symptoms or diffuse lung disease.
- Experts in the evaluation and management of suspected CBD have recommended a two-pronged approach: bronchoscopy to establish a definitive diagnosis and other testing to evaluate the clinical severity.
- Current diagnostic criteria for CBD require evidence of both BeS and disease (inflammation and granuloma formation).
- Patients with positive blood BeLPT results ideally should undergo bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy to look for evidence of pathology, which confirms the diagnosis.
- If the clinical suspicion remains high despite negative results on blood BeLPTs, consider referral to a pulmonologist with experience in the diagnosis and treatment of CBD for further evaluation.
- Further laboratory evaluation for a patient with a positive initial workup for CBD is performed to determine disease progression.

17. Patients with positive blood BeLPT results typically undergo

    A. Bronchoscopy.
    B. BAL.
    C. Transbronchial biopsy.
    D. All of the above.

To review relevant content, see "Overall Approach to the Workup of CBD" in this section.

How Should Patients Exposed to Beryllium Be Treated and Managed?

Learning Objective	Upon completion of this section, you will be able to • identify what patients should be treated, • identify the primary drug for treatment of chronic beryllium disease (CBD), and • describe possible sequelae of CBD.
Introduction	Although CBD is treatable, there is no cure for CBD. The goal of treatment is to reduce morbidity and mortality.
Who Should Be Treated?	For patients with impairing CBD, corticosteroid therapy continues to be the primary treatment modality (Glazer and Newman 2003). Patients who are sensitized to beryllium but do not yet have the disease do not need any treatment. However, they do need regular exams to detect early signs of disease, as well as early and aggressive treatment of respiratory infections. Patients who have early beryllium disease but do not yet have symptoms may not require treatment. However, they need to be medically monitored. Some people who are detected at the early stages may go many years without needing treatment. Patients with beryllium disease who have abnormal or deteriorating pulmonary functions are usually treated with prednisone.
Indications for Treatment	Indications for treatment include • severe disabling cough or dyspnea, • evidence of decline on resting pulmonary function tests, • worsening gas exchange abnormalities on exercise testing, or • signs of pulmonary hypertension and cor pulmonale (Lundgren *et al.* 2001; Maier 2002).
Treatment with Prednisone	Patients with evidence of early lung damage are treated with 40 mg of prednisone on a daily or alternate day regimen for 6 months. Prednisone is tapered by no more than 10 mg every other month to the lowest dose possible without evidence of renewed disease activity. Treatment with prednisone often stabilizes the disease and improves symptoms. Disease activity is monitored by the same tests that demonstrated deterioration. The lowest dose of prednisone that prevents disease progression should be maintained (Rossman 1996; Maier *et al.* 2001).
Monitoring the Disease	Unfortunately, lifelong therapy is usually required, since the disease recrudesces with reduction of the corticosteroid dose. Oral methotrexate and azathioprine have been used as corticosteroid-sparing agents by some clinicians (Glazer and Newman 2003; Muller-Quernheim *et al.* 1999). Before initiating corticosteroid therapy, a baseline chest radiograph, high resolution CT, complete pulmonary function tests (including lung volumes, spirometry, and diffusing capacity), and exercise testing, with arterial blood gas measurements, should be performed. Patients should be monitored for therapy-induced side effects on an ongoing basis.

Adjuvant Therapy	Adjuvant therapy with bronchodilators, diuretics, and oxygen should be considered as well. Supplemental oxygen may be necessary to correct hypoxemia associated with CBD. Right ventricular failure and its complications are late-stage sequelae. Pneumothorax can occur (Glazer and Newman 2003; Rossman 1996). Supportive therapy may also include pulmonary rehabilitation to maintain muscle strength and tone, vaccinations to prevent influenza and pneumococcal pneumonia, and antibiotics for acute infections.
Possible Sequelae and Management Considerations	Pulmonary fibrosis, which is common in long-term disease, is poorly responsive to corticosteroids. As with chronic lung disease of other etiologies, one should evaluate for bacterial respiratory infections and should treat infections promptly with antibiotics when indicated, especially for those on immunosuppressive therapy. Patients should be immunized against *Pneumococcus* and influenza and counseled to avoid exposures to other substances that cause lung injury, including cigarette smoke (Glazer and Newman 2003; Rossman 1996). Right ventricular failure and its complications are late-stage sequelae.
Importance of Early Detection and Treatment	In contrast to most occupationally related lung disease, the early detection of CBD is useful for several reasons. First, measures can be put in place to limit further beryllium exposure. Secondly, treatment can lead not only to regression of the signs and symptoms, but also should prevent further progression of the disease. The management of CBD is based on the hypothesis that suppression of the hypersensitivity reaction (the granulomatous process) will prevent the development of fibrosis. However, once fibrosis has developed, therapy cannot reverse the damage (Rossman 1996).
Preventive Measures	Primary preventive measures include skin protection and minimizing airborne exposures to prevent sensitization. Because beryllium sensitization (BeS) and CBD are immune-mediated processes, future exposures should be minimized for all affected patients and all workers. Some reports suggest that removal from exposure has lead to clinical improvement in select patients (Glazer and Newman 2003; Glazer and Newman 2004; Sood *et al.* 2004). It appears that BeS can occur after a short period of exposure, but beryllium disease may require a longer latency and/or period of exposure (Henneberger *et al.* 2001). The lack of a clear dose response for the development of CBD implies that early identification of sensitization and removal from exposure may reduce the development of CBD (Judd *et al.* 2003; Kelleher *et al.* 2001).
Dermatologic Management	Primary preventive measures such as avoiding skin contact with beryllium to prevent sensitization are key. Careful irrigation and debridement are recommended for wounds potentially contaminated with beryllium. Beryllium particles imbedded in the skin often must be removed before skin wounds will heal. Complete excision is curative for beryllium-contaminated injury sites that demonstrate delayed healing, ulceration, and granuloma formation. The main treatment for contact dermatitis associated with beryllium salt exposure is cessation of exposure (Berlin *et al.* 2003).

Key Points

- Primary preventive measures such as skin protection from and minimizing airborne exposures to beryllium are key to preventing sensitization.
- Primary prevention is far superior to medical treatment of CBD.
- Corticosteroid therapy is the primary treatment modality for CBD.

Progress Check

18. Indications for CBD treatment include which of the following?

    A. Evidence of decline on resting pulmonary function tests.
    B. Worsening gas exchange abnormalities on exercise testing.
    C. Signs of pulmonary hypertension and cor pulmonale.
    D. All of the above.

To review relevant content, see "Indications for Treatment" this section.

19. The primary drug for CBD treatment is

    A. Aspirin.
    B. Prednisone.
    C. MAO inhibitors.
    D. Acyclovir.

To review relevant content, see "Treatment with Prednisone" in this section.

20. What are possible sequelae or complications of CBD?

    A. Right ventricular heart failure.
    B. Pulmonary fibrosis.
    C. Pneumothorax.
    D. All of the above.

To review relevant content, see "Adjuvant Therapy" and "Possible Sequelae and Management Considerations" in this section.

Sources of Additional Information

Beryllium Specific Information

Please refer to the following Web resources for more information on the adverse effects of beryllium, the treatment of beryllium - associated diseases, and management of persons exposed to beryllium.

- Agency for Toxic Substances and Disease Registry (www.atsdr.cdc.gov)
  - For chemical, emergency situations
    - **CDC Emergency Response: 770-488-7100 and request the ATSDR Duty Officer**
  - For chemical, non-emergency situations
    - CDC-INFO (www.bt.cdc.gov/coca/800cdcinfo.asp)
    - 800-CDC-INFO (800-232-4636) TTY 888-232-6348 - 24 Hours/Day
    - E-mail: cdcinfo@cdc.gov

    Please Note: ATSDR cannot respond to questions about individual medical cases, provide second opinions or make specific recommendations regarding therapy. Those issues should be addressed directly with your health care provider.

  - ATSDR Minimal Risk Levels (www.atsdr.cdc.gov/mrls/)
  - ATSDR ToxFAQs™ - Beryllium: (www.atsdr.cdc.gov/tfacts4.html)
  - ATSDR Toxicological profile for beryllium. (www.atsdr.cdc.gov/tfacts4.html) Atlanta: U.S. Department of Health and Human Services; 2002, September.
  - ATSDR Toxic Substances and Health Brush Wellman Facility, Elmore, OH (www.atsdr.cdc.gov/sites/brushwellman)
- EPA Air Toxics - Beryllium: (www.epa.gov/ttn/atw/hlthef/berylliu.html)
- National Institute for Occupational Safety and Health (NIOSH). Pocket Guide to Chemical Hazards (www.cdc.gov/niosh/npg/). U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. Cincinnati, Ohio. February, 2004.
- National Institute for Occupational Safety and Health (NIOSH). NIOSH Safety and Health Topic – Beryllium. (www.cdc.gov/niosh/topics/beryllium/default.html)
- National Jewish Medical Center, 1-800-222-LUNG (1-800-222-5864) (www.nationaljewish.org/medfacts/beryllium_medfact.html).
- OSHA Safety and Health Topic - Beryllium. (www.osha.gov/SLTC/beryllium/index.html).
- U.S. Environmental Protection Agency. Toxicological Review of Beryllium and Compounds (www.epa.gov/iris/subst/0012.htm) In support of summary information on IRIS. National Center for Environmental Assessment, Washington, DC. 1998.

General Environmental Health Information

Please refer to the following Web resources for general information on environmental health.

- Agency for Toxic Substances and Disease Registry (www.atsdr.cdc.gov)
  - Taking an Exposure History CSEM (www.atsdr.cdc.gov/csem/exphistory/)
  - To view the complete library of CSEMs (www.atsdr.cdc.gov/csem/).
  - Exposure History Form (www.atsdr.cdc.gov/csem/exphistory/ehexposure_form.html)
  - ATSDR Division of Regional Operations.
    - Through the working relationships they have established with EPA, other federal and state agencies, individual citizens, and community groups, regional representatives are able to maintain current and historic knowledge of the sites and issues in their regions.
    - ATSDR's Regional Offices, along with the states and territories that they cover as well as contact information, can be found at www.atsdr.cdc.gov/DRO/dro_contact.html
  - ATSDR State Cooperative Agreement Program (www.atsdr.cdc.gov/states/atsdrstaff.html)
    - The Cooperative Agreement Program provides essential support in communities nationwide to fulfill the mission of the Agency for Toxic Substances and Disease Registry (ATSDR). The program funds 30 states and one tribal government to develop and strengthen their abilities to evaluate and respond to environmental public health issues.
- Centers for Disease Control and Prevention (CDC)(www.cdc.gov)
  - The CDC works to protect public health and the safety of people, by providing information to enhance health decisions, and promotes health through partnerships with state health departments and other organizations.
  - The CDC focuses national attention on developing and applying disease prevention and control (especially infectious diseases), environmental health, occupational safety and health, health promotion, prevention and education activities designed to improve the health of the people of the United States.
  - National Center for Environmental Health (NCEH) (www.cdc.gov/nceh/)
    - NCEH works to prevent illness, disability, and death from interactions between people and the environment. It is especially committed to safeguarding the health of

populations that are particularly vulnerable to certain environmental hazards - children, the elderly, and people with disabilities.

- NCEH seeks to achieve its mission through science, service, and leadership.

- National Institute of Occupational Safety and Health (NIOSH) (www.cdc.gov/niosh/)

  - NIOSH is part of CDC and was established to help assure safe and healthful working conditions for working men and women by providing research, information, education, and training in the field of occupational safety and health.

- National Institute of Health (NIH) (www.nih.gov)

  - A part of the U.S. Department of Health and Human Services, NIH is the primary Federal agency for conducting and supporting medical research.

- American College of Occupational and Environmental Medicine (ACOEM) (www.acoem.org)

  - ACOEM is the nation's largest medical society dedicated to promoting the health of workers through preventive medicine, clinical care, research, and education.

  - Its members are a dynamic group of physicians encompassing specialists in a variety of medical practices is united via the College to develop positions and policies on vital issues relevant to the practice of preventive medicine both within and outside of the workplace.

- American College of Medical Toxicologists (ACMT) (www.acmt.net)

  - ACMT is a professional, nonprofit association of physicians with recognized expertise in medical toxicology.

  - The College is dedicated to advancing the science and practice of medical toxicology through a variety of activities.

- American College of Preventive Medicine (ACPM) www.acpm.org

  - ACPM is the national professional society for physicians committed to disease prevention and health promotion.
  - ACPM's 2,000 members are engaged in preventive medicine practice, teaching and research.

- Association of Occupational and Environmental Clinics (AOEC) www.aoec.org

  - AOEC is a network of more than 60 clinics and more than 250 individuals committed to improving the practice of occupational and environmental medicine through information sharing and collaborative research.

- Pediatric Environmental Health Specialty Units (PEHSUs) www.pehsu.net

  - Each PEHSU is based at an academic center and is a collaboration between the pediatric clinic and the (AOEC) occupational and environmental clinic at each site.
  - The PEHSU's have been developed to provide education and consultation for health professionals, public health professionals and others about the topic of children's environmental health.
  - The PEHSU staff is available for consultation about potential pediatric environmental health concerns affecting both the child and the family. Health care professionals may contact their regional PEHSU site for clinical advice.

- Poison Control Center

  - The American Association of Poison Control Centers (AAPCC) may be contacted for questions about poisons and poisonings. The web site provides information about poison centers and poison prevention. AAPCC does not provide information about treatment or diagnosis of poisoning or research information for student papers.

  - American Association of Poison Control Centers (1-800-222-1222 or www.aapcc.org).

Suggested Reading

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Laboratories That Run the Beryllium Lymphocyte Proliferation Test

(Note: Use of trade names and commercial sources is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry or the U.S. Department of Health and Human Services.)

Cleveland Clinic Foundation Department of Clinical Pathology, L40 www.clevelandclinic.org/pathology/	9500 Euclid Avenue Cleveland, OH 44195-0001	Ph: (216) 444-2200 or 1-800-223-2273, ext 48844 or 55763 Fax: (216) 445-8160
National Jewish Center for Immunology and Respiratory Medicine Cellular Immunology Tests Pulmonary Division and Occupational/ Environmental Medicine Division www.nationaljewish.org/disease-info/diseases/occ-med/beryllium/	1400 Jackson Street Denver, CO 80206	Ph: (303) 398-1344

Hospital of the University of Pennsylvania Pulmonary Immunology Laboratory 833 BRB II/III pennhealth.com/lung/services/sarc.html	421 Curie Boulevard Philadelphia, PA 19104-4283	Ph: (215) 573-9906 Fax: (215) 349-5172
Specialty Laboratories, Inc. OncQuest www.specialtylabs.com/	2211 Michigan Avenue Santa Monica, CA 90404-3900	Ph: (310) 828-6543 or 1-800-421-4449

Other CSEMs *Case Studies in Environmental Medicine: Beryllium Toxicity* is one monograph in a series. For other publications in this series, please go to

www.atsdr.cdc.gov/csem/

Posttest Instructions

Introduction

ATSDR seeks feedback on this course so we can asses its usefulness and effectiveness. We ask you to complete the assessment questionnaire online for this purpose.

In addition, if you complete the assessment and posttest online, you can receive continuing education credits as follows.

Accrediting Organization	Credits Offered
Accreditation Council for Continuing Medical Education (ACCME)	The Centers for Disease Control and Prevention (CDC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of **1.5** *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.
American Nurses Credentialing Center (ANCC), Commission on Accreditation	This activity for **1.5** contact hours is provided by the Centers for Disease Control and Prevention, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.
National Commission for Health Education Credentialing, Inc. (NCHEC)	CDC is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. The Centers for Disease Control and Prevention is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the Certified Health Education Specialist (CHES) to receive **1.5** Category I contact hours in health education, CDC provider number GA0082.
International Association for Continuing Education and Training (IACET)	The Centers for Disease Control and Prevention (CDC) has been reviewed and approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), Suite 800, McLean, VA 22102. CDC will award **0.15** of CEU's to participants who successfully complete this program.

Disclaimer

In compliance with continuing education requirements, all presenters must disclose any financial or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters as well as any use of unlabeled product(s) or product(s) under investigational use.

CDC/ATSDR, our planners, and the presenters for this seminar do not have financial or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. This presentation does not involve the unlabeled use of a product or product under investigational use.

Instructions

To complete the assessment and posttest, go to www2.cdc.gov/atsdrce/ and follow the instructions on that page.

You can immediately print your continuing education certificate from your personal transcript online. No fees are charged.

Posttest

Click on the correct answers. There may be more than one correct answer for each question.

1. The following are true regarding beryllium except

   A. Beryllium is one of the heaviest metals known.
   B. Pure beryllium is a naturally occurring hard, grayish material obtained from mineral rocks bertrandite and beryl.
   C. The major source of its emission into the environment is combustion of fossil fuels.
   D. Beryllium is relatively water insoluble and adsorbs tightly to soils.

2. Which of the following activities are potential sources of beryllium exposure?

   A. Fabricating aircraft/satellite structural components.
   B. Washing the clothes of a machinist.
   C. Applying fertilizers.
   D. Traveling in an airplane.
   E. Grinding dental prostheses.

3. A worker's family members may be exposed to beryllium by

   A. Sharing utensils with the worker.
   B. Kissing the worker.
   C. Gathering and washing the workers dirty clothes.
   D. Living beneath high-voltage power lines.

4. It is a federal (OSHA) regulation that workers not be exposed to more than 2 $\mu g/m^3$ of beryllium in air

   A. Averaged over an 8-hour workday.
   B. At any time during the day.
   C. If they have underlying lung disease.
   D. If they are not wearing a paper dust mask.

5. The EPA regulation for beryllium emissions in air is

   A. 10 micrograms in a 24-hour period.
   B. 10 grams in a 24-hour period.
   C. 10 grams averaged over an 8-hour workday.
   D. 10 micrograms averaged over an 8-hour workday.

6. Which of the following statements are true?

   A. Ingestion of beryllium is associated with high rates of chronic beryllium disease.
   B. Beryllium is classified by some agencies as a known carcinogen in humans.
   C. Some individuals have a genetic susceptibility to beryllium sensitization or disease.
   D. Skin contact with ultrafine beryllium particles may cause disease.
   E. People who have chronic beryllium disease should be considered infectious.

7. Which of the following are correct?

   A. In beryllium sensitization and chronic beryllium disease, a susceptible person develops a cell-mediated, delayed hypersensitivity reaction after beryllium exposure.
   B. Both individual susceptibility and exposure circumstances are important in developing chronic beryllium disease.
   C. The *HLA-DPβ1* genes with the supratypic marker Glu69 may lead to an increased risk for those exposed to beryllium.
   D. All of the above.

8. Possible chest radiograph findings associated with beryllium–related diseases may include

   A. Nodular diffuse infiltrates.
   B. Diffusely linear infiltrates.
   C. Hilar adenopathy
   D. All of the above.

9. Which of the following statements are true?

   A. Acute and chronic beryllium disease results from the same physiologic mechanism.
   B. Acute beryllium disease can progress to chronic beryllium disease.
   C. The distinguishing feature of acute beryllium disease is the presence of granulomas.
   D. Today, acute beryllium disease is a rare occurrence in the workplace.
   E. Chronic beryllium disease predominantly affects the lungs and skin.

10. Exposure to beryllium may result in which of the following conditions?

   A. Contact dermatitis.
   B. Ulcerative granulomas.
   C. Emphysema.
   D. Interstitial pneumonitis.
   E. Hypersensitivity.

11. Which of the following statements are true?

    A. The period between initial beryllium exposure and detectable disease can be less than one year.
    B. Sarcoidosis and chronic beryllium disease have certain manifestations that are similar.
    C. Pulmonary function tests and a chest radiograph can be used to distinguish a patient with sarcoidosis from one with chronic beryllium disease.
    D. Cutaneous granulomas result from beryllium inhalation only.
    E. Most patients with chronic beryllium disease require steroid therapy for less than one year.

12. Tests that may be used to distinguish beryllium sensitization from CBD include

    A. Pulmonary function tests.
    B. Chest radiography.
    C. Blood BeLPT.
    D. Diffusion capacity for carbon monoxide.
    E. Arterial-alveolar gradient at rest.

13. Tests that may be used to distinguish sarcoidosis from chronic beryllium disease include

    A. Pulmonary function tests.
    B. Blood BeLPT.
    C. Bronchoalveolar lavage BeLPT.
    D. Serum alpha fetoprotein level.
    E. None of the above.

14. Proper treatment and management of chronic beryllium disease might include

    A. Pneumococcal immunization.
    B. Influenza immunization.
    C. Corticosteroid therapy.
    D. Excision of beryllium-contaminated cutaneous sites.

15. Indications for CBD treatment include which of the following?

    A. Evidence of decline on resting pulmonary function tests.
    B. Worsening gas exchange abnormalities on exercise testing.
    C. Signs of pulmonary hypertension and cor pulmonale.
    D. All of the above.

16. What are possible sequelae or complications of CBD?

    A. Right ventricular heart failure.
    B. Pulmonary fibrosis.
    C. Pneumothorax.
    D. All of the above.

Relevant Content	To review content relevant to the posttest questions, see:

Question	Location of Relevant Content and Learning Objective
1	Where is beryllium found? • Describe beryllium properties
2	How are people exposed to beryllium? • Describe how people are exposed to beryllium Who is at risk of exposure to beryllium? • Identify the populations most heavily exposed to beryllium
3	Who is at risk of exposure to beryllium? • Identify who is at risk of exposure to beryllium in the home
4	What are standards and regulations for beryllium exposure? • Describe the OSHA permissible exposure limit (PEL) for Beryllium
5	What are standards and regulations for beryllium exposure? • Describe the EPA regulation for Beryllium emissions in air
6	Who is susceptible to beryllium exposure? • Name a marker of genetic susceptibility to beryllium exposure How does beryllium induce pathogenic changes? • Describe health conditions associated with beryllium exposure
7	Who is susceptible to beryllium exposure • Name a marker of genetic susceptibility to beryllium exposure How does beryllium induce pathogenic changes? • Describe two mechanisms of injury resulting from beryllium exposure
8	Clinical assessment • Describe chest radiograph findings associated with beryllium-related diseases

9	How does beryllium induce pathogenic changes? • Describe two mechanisms of injury resulting from beryllium exposure • Describe health conditions associated with beryllium exposure
10	How does beryllium induce pathogenic changes? • Describe health conditions associated with beryllium exposure
11	Clinical assessment • Describe pulmonary function test findings associated with beryllium-related diseases • Describe chest radiograph findings associated with beryllium–related diseases
12	Clinical assessment • Describe pulmonary function test findings associated with beryllium-related diseases • Describe chest radiograph findings associated with beryllium–related diseases Clinical assessment – other diagnostic tests • Identify other tests that can assist with diagnosis of beryllium-related diseases
13	Clinical assessment – other diagnostic tests • Identify other tests that can assist with diagnosis of beryllium related diseases
14	How should patients exposed to beryllium be treated and managed? • Identify the primary drug for treatment of chronic beryllium disease (CBD)
15	How should patients exposed to beryllium be treated and managed? • Identify what patients should be treated
16	How should patients exposed to beryllium be treated and managed? • List possible sequelae of chronic beryllium disease

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