LEAD POISONING

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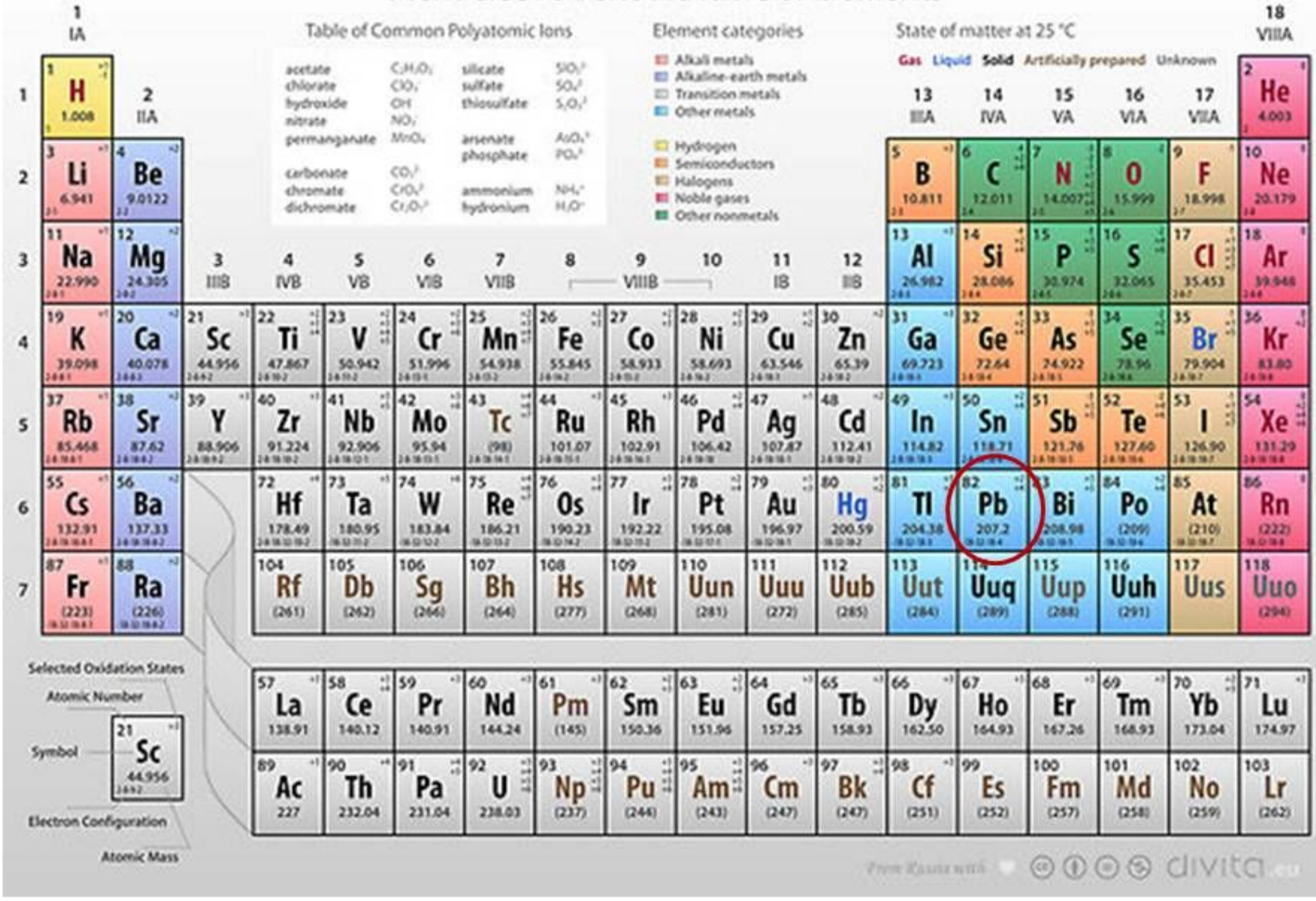
Mendeleev's Periodic Table of Elements



HISTORY

Lead has been mined for thousands of years, the earliest recorded lead mine reportedly existed in Turkey in 6500 BC.

- Evidence high lead use can be found in the skeletons of ancient Egyptians.
- By the Greek Bronze Age, lead was widely used in the manufacture of brass and cosmetics.
- Romans used lead in their plumbing, cooking utensils and in the vessels concentrated grape juice for wine.

HISTORY

- Hippocrates wrote descriptions of lead colic.
- Initial interest in the illness: in 1839 by Tanquerel des Plances in workers, painters with lead colic.
- Childhood lead poisoning was first reported in Brisbane, Australia, in 1899.
- In 1943, Byers and Lord indicated no obvious sequelae: cognitive disturbances or frank mental retardation, intelligence, hyperactivity…

HISTORY

- In 1959, the U.S. Public Health Service recommended: BLL 60-80µg/dL: evidence of increased lead absorption in children.
- In 1970, the Surgeon General reduced to:40µg/dL
- In 1975, CDC began to establish classifications for children lead poisoning:
  - 30µg/dL in 1975
  - 25 µg/dL in 1985 and 10 µg/dL in 1991
  - the 97.5th percentile of blood lead levels in US children: 5µg /dL as of 2012.

EPIDEMIOLOGY

- An estimated 450, 000 children in the US were above 5µg/dL in 2012.
- The peak onset of lead poisoning in children is the second year of life.
- Children younger than 6 year of age are more susceptible to the toxic effects of lead, because of:
  - INCOMPLETE BLOOD-BRAIN BARRIER
  - A GREATER PREVALENCE OF IRON DEFICIENCY
  - GREATER RISK OF EXPOSURE TO LEAD DUST BECAUSE OF CRAWLING AND HAND-TO-MOUTH BEHAVIOR)

SOURCES

- Children typically are exposed to environmental lead through ingestion or inhalation.
- Common sources:
  - chips of paint or lead dust from lead-painted surfaces
  - food or beverages purchased, stored, or served in lead-soldered cans or lead-glazed pottery
  - water from lead-soldered plumbing
  - automobile emissions
  - lead-using industry.
- Less common sources:
  - herbal and folk medications
  - crayons and other toys
  - cosmetics
  - cookware.

TOXICOLOGY

- The absorption of lead depends upon:
  - the route of exposure
  - the age and nutritional status of the exposed individual .
- Lead that is inhaled into the lower respiratory tract is absorbed completely.
- Children absorb a greater proportion of lead from the gastrointestinal tract than do adults (up to 70 percent versus 20 percent). Fasting, iron and calcium deficiency: increase the gastrointestinal absorption of lead.

TOXICOLOGY

- Lead is distributed in the blood, soft tissues and mineralized tissues(bones and teeth)
- The half- life of lead varies depending upon the body compartment:
  - Blood: 28 to 36 days
  - Soft tissues: 40 days
  - Mineralized tissues: >25 years

TOXICOLOGY

- Lead:
  - not retained in the tissues
  - excreted by the kidneys or through biliary clearance into the gastrointestinal tract.
- Children < 2 years of age retain approximately one-third of absorbed lead whereas adult 1%.
- > 70% of the total body burden of lead in children: contained in the mineralized tissues

→THE BLL IS NOT A GOOD REFLECTION OF THE TOTAL BODY LEAD BURDEN

TOXICOLOGY

- The lead in mineralizing tissue accumulates in 2 compartments:
  - A labile compartment: readily exchanges lead with the blood
  - A inert pool: lead can be mobilized during periods of physiologic stress and represents an endogenous source of lead that can maintain an elevated BLL long after the exogenous exposure source has been removed.

MOLECULAR TOXICOLOGY

Lead interferes with the interactions of divalent cations and sulfhydryl groups whereas most biochemical reactions are regulated by these agents.

- In vitro, many of the reactions in which lead serves as a competitive inhibitor are reversible
- In vivo, downstream events lead to cell death and irreversible damage, particularly in the central nervous system.

MOLECULAR TOXICOLOGY

Lead can disrupt signal transduction cascades by :

- Activating protein kinase C
- Competing with magnesium
- Inhibiting cyclic nucleotide hydrolysis by phosphodiesterases, or inhibiting function at the N- Methyl- D- Aspartate type Glutamate receptor.
- Lead also can uncouple mitochondrial oxidative phosphorylation in the central nervous system.

MOLECULAR TOXICOLOGY

- Magnetic resonance spectroscopy in individuals with elevated BLL demonstrates reduction in the N- Acetylaspartate/ Creatine and Phosphocreatine ratios in the frontal gray matter, suggesting that lead poisoning affects metabolism in the brain.

MOLECULAR TOXICOLOGY

Lead competes with calcium for entry into synaptosomes and interacts with numerous receptor-activated and voltage-gated cation channels.

Lead increases the infidelity of DNA and RNA polymerase→somatic and germline mutations.

MOLECULAR TOXICOLOGY

- Hematologic complications:
  - Directly inhibit δ-aminolevulinic acid synthetase (ALAS) and δ-aminolevulinic acid dehydratase (ALAD), enzymes necessary for heme biosynthesis, and ferrochelatase, a mitochondrial sulfhydryl enzyme.
  - Inhibition of ferrochelatase results in an increased level of zinc protoporphyrin in the blood.
  - Inhibit pyrimidine 5' nucleotidase activity→ the basophilic stippling sometimes observed in erythrocytes

CLINICAL MANIFESTATIONS

- vary depending upon the lead exposure and the age
- some children with severely elevated BLL≥ 250 µg/dl may be asymptomatic.
- early symptoms of acute:
  - episodic and nonspecific
  - anorexia, decreased activity, irritability, insomnia.
- The symptoms slowly intensify over time.

CLINICAL MANIFESTATIONS

- **Neurologic:**
  - The developmental delay or loss of milestones, particularly in language, encephalopathy, hearing loss, peripheral neuropathy, and decreased nerve conduction velocity, cerebral edema
  - Lead levels≥ 10µg/dL affect the cognitive and behavioral development:
    - **Neurocognitive effects also have been demonstrated at even lower BLLs and no known threshold.**
    - **Neurobehavioral appear to persist, at least in part, into adolescence, despite a decline in BLL.**
  - Lead encephalopathy may develop inappropriate antidiuretic hormone secretion

CLINICAL MANIFESTATIONS

- Hematologic:
  - rarely results in anemia
  - Anemia secondary to lead toxicity usually is mild, hemolytic, and normocytic.
    - In contrast, anemia secondary to iron deficiency is hypochromic, microcytic, and reticulocytopenic.
- Partial heart block, and marked decrease in renal function.

CLINICAL MANIFESTATIONS

- **Renal:**
  - Lead nephropathy (characterized histologically by chronic interstitial nephritis, is a potential complication of prolonged high-level lead exposure)
- **Gastrointestinal:**
  - Lead colic
  - Sporadic vomiting
  - Intermittent abdominal pain
  - Constipation

  (may occur with a BLL as low as 60 µg/dL)

CLINICAL MANIFESTATIONS

- Endocrine
  - Vitamin D metabolism is decreased at BLL of 30 µg/dL.
  - On cell growth, maturation and tooth and bone development probably are mediated through the effects on vitamin D.
  - Mildly elevated BLL may affect pubertal development.

DIAGNOSIS

- Lead poisoning is diagnosed in the United States when the venous blood lead level is greater than 97.5th percentile for the pediatric population (5 µg/dL in 2012).

DIAGNOSIS

- Acute encephalopathy of unknown etiology + BLL cannot be obtained immediately → clinical findings:
  - Strongly positive qualitative urine coproporphyrin
  - Basophilic stippling of peripheral RBC or erythroblasts in the bone marrow.
  - Hypophosphatemia
  - Glycosuria
  - Lead flecks on abdominal radiograph
  - Lead lines on long-bone radiographs

DIAGNOSIS

- Children with lead encephalopathy:
  - ↑ blood erythrocyte protoporphyrin (EP) or zinc protoporphyrin (ZPP) concentrations (>35 µg/dL).
  - detection of δ-aminolevulinic acid levels in the urine

EVALUATION

- **History:**
  - Onset and severity of symptoms of toxicity
  - Nutritional history (intake of iron and calcium +++)
  - History of pica
  - Family history of lead poisoning
  - Assessment of potential sources of lead exposure
- **Physical examination:**
  - The possible neurologic consequences of lead toxicity
  - Lead lines
- **Laboratory evaluation:**
  - Lead levels: should **repeat BLL** to confirm the diagnosis
  - Additional tests: CBC, reticulocyte count, serum iron, iron binding capacity, ferritin
  - Serum electrolytes, BUN, creatinine, calcium, magnesium, transaminases, and urinalysis.
  - G6PD

EVALUATION

- Severe intoxication:
  - BLL ≥70 µg/dl or having symptoms of encephalopathy
- Moderate intoxication:
  - BLL 45- 69 µg/dL and the absence of symptoms
- Mild intoxication: ≤44µg/dl
  - BLL 20 to 44 µg/dL
  - BLL 15 to 19 µg/dL
  - BLL 5 to 14 µg/dL
  - BLL <5 µg/dL

TREATMENT

- Treatment depends upon:
  - the degree of the blood lead elevation
  - the presence of symptoms.
- 3 components, in descending order of importance:
  - Enviromental inspection/hazard reduction
  - Nutritional supplementation
  - Chelation therapy

TREATMENT

- Breastfeeding should be encouraged for all mothers with a BLL <40 µg/dL.
  - Infant monitoring of BLL during breastfeeding.
- In a child with acute lead ingestion: placing an orogastric or nasogastric catheter to enable whole-bowel irrigation (WBI) with polyethylene glycol.

TREATMENT

- Education +++
- Nutrition
  - Regular meals and adequate calcium and iron intake
  - Intestinal lead absorption is increased during periods of fasting
  - Adequate intake of vitamin C may increase the renal excretion of lead.

TREATMENT

- Goal for chelation therapy:
  - reduce BLL to the range of 10-15µg/dL
  - long- term treatment strategies and frequent monitoring.
- Chelating agents remove lead from the blood and soft tissues, including the brain.

TREATMENT

- Dimercaprol increases the urinary excretion of heavy metals through the formation of stable, nontoxic, soluble chelates.
- Calcium disodium EDTA: a second chelating agent ($CaNa_2EDTA$, Edetate Disodium Calcium), is similar to dimercaprol, increases the urinary excretion of lead through the formation of a nonionizing, soluble chelate.

TREATMENT

- DMSA — meso-2,3-dimercaptosuccinic acid (DMSA, succimer®):
  - is a water soluble analog of dimercaprol, can be administered orally.
  - increases the urinary excretion of lead. It was approved by the US FDA for use in children with BLL≥ 45 µg/dL in 1991.
  - has little toxicity.
  - is relatively specific for lead and causes less urinary loss of essential minerals.
  - may be administered concurrently with iron.
  - Adverse effects: rash, neutropenia, elevation of serum liver transaminases, and gastrointestinal upset, hemolysis in a patient with G6PD deficiency.

TREATMENT

- Severe intoxication: a medical emergency.
  - Chelation therapy can be life-saving.
  - Chelation therapy should be performed in consultation with a toxicologist or other clinician who has experience with the chelating agents:
    1. to control convulsions.
    2. an adequate flow of urine.
    3. to decrease the lead burden through administration of chelation therapy.

TREATMENT

- **Severe intoxication:**
  - Initial chelation therapy:

    dimercaprol (BAL) + calcium disodium edetate ($CaNa_2EDTA$)
    (Grade 1A)
  - Second course:
    - dimercaprol + $CaNa_2EDTA$: BLL is ≥70µg/dL
    - Dimercaptosuccinic acid (DMSA) may be used in asymptomatic children who have BLLS: 45 – 70 µg/dL
    - A minimum of two days without treatment should occur between the first and second courses.
  - Third course:
    - If BAL ≥ 45 µg/dL
    - 5 – 7 days after the second course

TREATMENT

- MODERATE INTOXICATION:

  BLL 45- 69 µg/dL + the absence of symptoms related to lead toxicity.

  ➔Chelation therapy should begin as soon as possible after the BLL is confirmed.

TREATMENT

- MODERATE INTOXICATION:

Chelation therapy: orally or parenterally.

Factors to be considered in this decision include:

- Age of the child
- Likelihood of compliance with an oral regimen
- Duration of lead toxicity
- Susceptibility to renal or hepatic toxicity
- Hypersensitivity to sulfa or penicillin drugs
- Indications for hospitalization

TREATMENT

- MODERATE INTOXICATION:
  - shoud receive chelation with DMSA until the BLL is <45 µg/dl.
  - For children who cannot adhere to treatment with oral DMSA, continuous infusion of $CaNa_2EDTA$ may be used instead.(Grade 2B).

TREATMENT

- MODERATE INTOXICATION:

  The efficacy of intravenous $CaNa_2EDTA$ and oral DMSA therapy in the treatment of moderate lead toxicity were compared in a controlled trial of 19 hospitalized children:

  – DMSA was more effective in reducing mean BLL after five days of therapy (61% versus 45 %) and was well tolerated.
  – BLL 14 days after discharge depended upon outpatient therapy:
    - **73 % of pretreatment levels with no additional therapy,**
    - **66 5 % of pretreatment levels with low-dose DMSA (350 mg/m^2 per day),**
    - **and 50 % of pretreatment levels with high-dose DMSA (750 mg/m^2 per day).**

TREATMENT

- DMSA is given at a dose of 10 mg/kg or 350 mg/m^2 (rounded to the nearest 100 mg) three times per day for five days followed by the same dose two times per day for 14 days.
- At approximately five years of age, mg/kg dose and the mg/m^2 doses are equivalent; for younger children, calculations based on body surface area provide higher doses, which are recommended.

TREATMENT

- MILD INTOXICATION (≤44µg/dl):

four categories of mild lead intoxication have been defined:

- **Venous BLL 20 to 44 µg/dL**
- **Venous BLL 15 to 19 µg/dL**
- **Venous BLL 5 to 14 µg/dL**
- **Detectable venous BLL <5 µg/dL**

20 to 44 µg/dL:

- **parent education**
- **ntritional counseling**
- **notification of public health authorities for environmental surveillance**
- **remediation.**

TREATMENT

- **MILD INTOXICATION:**
  - Children with BLL in the range of 20 - 44 µg/dL shoud receive outpatient chelation with oral DMSA. (Grade 2C).
  - Chelating children with (BLLs) in the range of 20- 44 remains controversial.

TREATMENT

- **MILD INTOXICATION:**

The effects of as many as three courses of DMSA therapy were evaluated in a double-blind, randomized, placebo-controlled trial in 780 children (aged 12 to 33 months) BLL of 20 to 44 µ/dL. Cognitive, motor, behavioral, and neuropsychologic functions were followed over a period of 36 months, and again at age seven years.

TREATMENT

- **MILD INTOXICATION:**

  The following results were obtained:

  - **Mean BLL in the treatment group was 4.5 µg/dL (95% CI, 3.7-5.3 µg/dl) lower than that in the placebo group during the first 6 months of the trial.**
  - **The mean IQ score of children in the treatment group was one point lower than that of children in the placebo group.**
  - **The behavior of the children, as rated by a parent, was slightly worse in the treatment than in the control group. Children in the treatment groups scored slightly better on a battery of tests designed to measure neuropsychologic deficits thought to interfere with learning; these differences were small and not statistically significant.**
  - **At seven years of age: no statistically significant differences were observed between treatment and control groups in the areas of cognition, behavior, learning, memory, attention, or neuromotor performance.**

TREATMENT

- **MILD INTOXICATION:**
  - The authors conclude that:
    - although chelation therapy in general, and DMSA in particular, is effective in lowering BLLs in children with BLLs less than 45 µg/dL, it does not improve scores on tests of cognition, behavior.
    - although chelation treatment with DMSA may not result in reversal of CNS damage that already has occurred it may prevent further damage.

  → continues to provide chelation therapy to children with BLLs in the range of 20 to 44 µg/dL

TREATMENT

- D-penicillamine: another oral chelating agent.
  - APP guidelines : as a third-line agent.
  - only when unacceptable reactions have occurred to DMSA or $CaNa_2EDTA$, and continued therapy is required for moderate intoxication or is desired for children with BLLS of 20 to 44 μg/dL.
  - D-penicillamine increases the urinary excretion of lead. The absorption of D-penicillamine is inhibited by iron, aluminum- and magnesium-containing antacids, and food.
  - Adverse effects: nausea and vomiting, transient leukopenia, thrombocytopenia, rash, enuresis, abdominal pain, hematuria, abnormal liver function, angioedema, urticaria, or maculopapular rash, ↑ the urinary excretion of zinc, pyridoxine, and iron.
  -

TREATMENT

- D-penicillamine :
  - The efficacy of D-penicillamine (25 to 35 mg/kg/ day) in the management of children with low BLL between 25 - 40 µg/dL was evaluated in a retrospective cohort study comparing children (≈ 3 years) who were and were not treated with penicillamine therapy. Mean BLL in the treatment group declined by 33 percent (from 34 to 22 µg/dL and did not change in the control group (34 to 32 µg/dL).
  - Treatment failure occurred in 10% and adverse effects in 33%. Adverse reactions prompted discontinuation of therapy in 10 percent of patients. Reducing the dose of D-penicillamine to 15 mg/kg/day appears to decrease the rate of adverse reactions without affecting the efficacy to reduce BLL in children with mild to moderate lead toxicity .

TREATMENT

- Children with BLLs 5 – 19 µg/dL should have a confirmatory BLL within one month.
- A repeat BLL should be obtained within 3 ms.

TREATMENT

- Children with detectable BLL <5 µg/dL are at risk for neurocognitive deficits. All children should be monitored regularly for developmental and behavioral problems, no matter what their BLL.
- Another chelator, 2,3-dimercaptopropane-1-sulfonic acid sodium salt (DMPS), is available in Europe both orally and parenterally. It has not been approved or licensed in the United States, but it has been used in various forms in alternative medicine clinics.

PREVENTION

- removal of lead from the environment
- minimize absorption of lead and deposition in the mineralizing tissues.
- reduce the morbidity associated with lead intoxication through chelation of lead from the blood and soft tissues of an exposed individual.


Persistent growth arrest lines in a child with prior lead poisoning


Gingival lead line in adult with lead poisoning

REFERRNCES

- UpToDate
- Medscape
- Cochrane Library
- Michael W. Shannon, Stephen W. Borron, Michael J. Burns. (2007), “Haddad and Winchester’s Clinical Management of POISONING AND DRUG OVERDOSE” SAUDERS Elsevier, 4th edit,pp.1129-1146

BỘ Y TẾ	CỘNG HÒA XÃ HỘI CHỦ NGHĨA VIỆT NAM
———	**Độc lập - Tự do - Hạnh phúc**
	———
Số: 1548/QĐ-BYT	*Hà Nội, ngày 10 tháng 5 năm 2012*

QUYẾT ĐỊNH
VỀ VIỆC BAN HÀNH HƯỚNG DẪN CHẨN ĐOÁN VÀ ĐIỀU TRỊ NGỘ ĐỘC CHÌ
BỘ TRƯỞNG BỘ Y TẾ

Căn cứ Nghị định số 188/2007/NĐ-CP ngày 27 tháng 12 năm 2007 của Chính phủ quy định chức năng, nhiệm vụ, quyền hạn và cơ cấu tổ chức Bộ Y tế;

Xét biên bản họp ngày 3/5/2012 của Hội đồng chuyên môn xây dựng Hướng dẫn chẩn đoán và điều trị ngộ độc chì;

Theo đề nghị của Cục trưởng Cục Quản lý khám, chữa bệnh – Bộ Y tế,

QUYẾT ĐỊNH:

Điều 1. Ban hành kèm theo Quyết định này Hướng dẫn chẩn đoán, điều trị ngộ độc chì.

Điều 2. Quyết định này có hiệu lực kể từ ngày ký, ban hành.

Điều 3. Các ông, bà: Chánh Văn phòng Bộ; Chánh Thanh tra Bộ; các Vụ trưởng, Cục trưởng của Bộ Y tế; Giám đốc các bệnh viên, viện có giường bệnh trực thuộc Bộ Y tế; Giám đốc Sở Y tế các tỉnh, thành phố trực thuộc Trung ương; Thủ trưởng y tế các Bộ, ngành; Thủ trưởng các đơn vị có liên quan chịu trách nhiệm thi hành Quyết định này./.

BỘ TRƯỞNG

Nơi nhận:
- Như Điều 3;
- Các Thứ trưởng (để biết);
- Website Bộ Y tế, website Cục QLKCB;
- Lưu: VT, KCB.

Nguyễn Thị Kim Tiến

Clinical case

- Patient's name: Ng. Q. K.
- Date of birth: 28/12/2008 (46 months)
- Address of residence: An Thoi ward, Phu Quoc District, Kien Giang province
- Date of admission: 31/07/2012
- Reason of admission: coming to Nhi Dong 2 to be treated lead poisoning.

Clinical case

- History:
  - The child was taken lead folk medication by his parents to treat cough, runny nose, sore throat during 9 months in 2 years before.
  - The patient ' parents found his abnormal behavior: hyperactivity, difficult in concentrating and he is slower than his sister in cognitive and doing something.
  - The parents took him to Bach Mai hospital to be tested BLL after hearing notice on TV about lead poisoning.
  - They took his child to Nhi Dong 2 to be treated with the result of BLL 32.85 µg/dL (5/7/2012).

Clinical case

- Body weight: 15 kgs, Height: … cm
- Psychiastry: moderate developmental delay
- Psychology: no abnormal signs
- Dr. Duệ (Bạch Mai Hospital' s director – Ha Noi): chelator therapy to decrease BAL into ≤ 10 µg/dL.

Clinical case

- On 1/8/2012 BLL rechecked: 38.9 µg/dL(36,4)
- Serum iron: 325 µg/dL (50-168)
- Ferritin: 29 ηg/ml (15-120)
- Liver and kidney function: normal
- Ionogram, chest X-ray, abdominal ultrasound: normal, CRP: 0 mg/l
- CBC, PLT: normal, HCT=34,4%, Hgb=12,1g/dL, MCV= 73,1fl, MCH=25,7pg, MCHC=35,5 g/dL

Clinical case

- The first Succimer therapy (… – 1/8/2012)

→ BLL= 24 µg/dL (…/8/2012)

- The second Succimer therapy (… – 1/9/2012):

→ BLL: 10,2 µg/dL (…/9/2012)

→ BLL: 27,3 µg/dL (…/10/2012)

- The third Succimer therapy: ?

Thanks for your attention