Lead Poisoning in Children
What’s new about an old problem?

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September, 2018
Lead In Children

- Today, at least 4 million households have children living in them being exposed to high levels of lead.
- Approximately, 500,000 children 1-5 years of age have blood lead level (BLL) > 5 µg/dL.
- No safe BLL in children has been identified.
- Lead exposure can affect every system in the body.
- Lead exposure frequently goes unrecognized as it often occurs with no obvious symptoms.
Epidemiology of Lead Poisoning

- CDC data (2014) indicate ~ 800 per 100,000 children < 1 yr of age and 8,000 per 100,000 children 1-4 yr of age have elevated BLL > 10 µg/dL
- CDC data (2014) has identified ~ 29,000 children < 5 years of age with BLL 5-9 µg/dL
- CDC data (2014) has identified ~ 500,000 children 1-5 years of age with BLL > 5 µg/dL—the reference level at which CDC recommends public health actions be implemented
- NHANES III data has identified characteristics of groups at increased risk of elevated BLLs
  - Preschool age
  - Lower socioeconomic status
  - Urban residence
  - African-American race
Mean blood lead level for Americans aged 1-74 yr. continued to decline
- 12.8 µg/dL in 1976-1980 to
- 2.9 µg/dL in 1988-1991 to
- 2.3 µg/dL in 1991-1994 to
- 1.6 µg/dL in 1999-2002

For children aged 1-5, lead poisoning rates declined similarly
- About 1.6% of children (310,000) had blood lead levels > CDC threshold of 10 µg/dL (CDC threshold now revised to 5 µg/dL with an estimated 535,000 or 2.6% children above this level)
- Down from 4.4% (900,000) in 1991-1994
Overall, 2.6% of children (approx. 535,000) aged 1-5 yr. are considered lead-poisoned.
Rates are highest for non-Hispanic black children aged 1-5 (3.1%).
For children aged 1-5, African-American race/ethnicity, low income, and living in pre-1946 housing were associated with elevated BLLs.
NHANES Update - Phase 3

Race

- Lead poisoning rates are higher among African-American (8.7%) than Mexican-American (5.6%) children and non-Hispanic white children (2.3%)
- Above indicates differences in risk for exposure still persist.
NHANES Update - Phase 3

Age of Housing

- Children living in pre-1946 housing had a 8.6% rate of lead poisoning
  - 4.6% of those in 1946-1973 housing
  - 1.6% of those in post-1973 housing
- Elevated risk by age of housing persisted across race, income, and urban status
- Risk was higher in African-American children living in pre-1946 housing (21.9%) or 1946-1973 housing (13.7%)
- Low-income children living in pre-1946 housing (16.4%)
- Urban children living in pre-1946 housing (11.6%)
Sources of Lead Poisoning in Children

Most common highly concentrated source of lead in children in the United States is lead paint

- Leaded Paint in Old Housing
  Federal regulations limited use of lead in household paint to <0.06% by weight - promulgated late 1970s

Pigment industry began decreasing lead in paint in 1950s

Prior to the 1950s, lead comprised up to 50% of the wt of paint - a 1-g paint chip (size of a fingernail) could contain 500 mg of lead
(For comparison, an average child can spontaneously excrete only up to 100 μg per day)
Sources of Lead Poisoning in Children

- Lead in Household Paint
  Paint that is peeling and flaking, thus becoming accessible for ingestion, poses an active risk for children (especially preschool children who traditionally have increased hand-mouth activity)

  Leaded paint on an intact surface is a potential risk for the future

  Leaded paint may be in the
  - Primary residence
  - A baby-sitter’s residence
  - Day-care center

- Lead dust from deteriorating paint
- Renovations causing lead-laden dust
Sources of Lead Poisoning in Children

- Leaded Paint in Old Housing
  Federal regulations limited use of lead in household paint to <0.06% by weight- promulgated late 1970s

  Pigment industry began decreasing lead in paint in 1950s

  Prior to the 1950s, lead comprised up to 50% of the wt of paint - a 1g paint chip (size of a fingernail ) could contain 500 mg of lead
  ( For comparison, an average child can spontaneously excrete only up to 100 μg per day )
Other Significant Sources of Lead Exposure

- Adults exposed to lead at work might bring home leaded dust on their clothes.
- Lead in pigments used by artists, potters, and glaziers (released from crockery, decanters into food).
- Soil and surface contamination that occurred during decades of leaded gasoline usage continues to contribute to background exposure.
- Lead in home-folk remedies (azarcon, greta, pay-loo-ah, ayurvedic medicine).
- Lead in food additives (lozeena), ethnic spices.
- Lead in ethnic cosmetics (kohl, surma, sindoor).
- More recently, lead in imported toys, candy from Mexico.
Water as a Source of Lead Poisoning

- Most municipal water supplies are relatively lead-free.
- Lead may be leached out as water flows through lead pipes or lead-soldered pipes, especially if acidic.
- Highest concentrations of lead in tap water are found in water standing in pipes overnight.
- Hot water has higher conc of leached lead.
- Allowing water to flow for a minute to 2 lowers the lead conc to acceptable levels ( <15 ppb or 15 ng of lead per g of water ).
- Hot water should not be used for cooking or drinking purposes or for preparation of formula.
- First draw not to be used for preparation of formula.
Water as a Source of Lead Poisoning

- A growing source of childhood lead exposure because of aging infrastructure
- Evident from ‘Flint Drinking Water Crisis’
- Incidence of elevated BLL increased from 2.4% to 4.9% in children younger than 5 years in children residing in Flint after water source change in April 2014
- Disadvantaged neighborhoods having the greatest elevated BLLs

Hanna-Attisha, LaChance, Sadler, Schnepp: AJPH 2015
Hazard of Lead in Infant Formula

Lead in drinking water - hazardous practices in preparing formula

- Use of water first-drawn in the morning
  “First-draw” water has the highest lead conc
- Excessive boiling of water
- Inadvertent use of lead-based kettles for boiling

Lead Absorption and Distribution

- Lead crosses the placenta freely - accumulation in the fetus results in a potentially toxic burden in infants of mothers with elevated blood lead levels.
- Postnatally, lead is absorbed primarily through the respiratory and gastrointestinal tracts.
- The relative absorption varies considerably and is affected by:
  - age
  - nutritional status
  - particle size
  - Route of exposure
  - chemical composition
Metabolism of Lead

- Absorption affected by:
  - Age: Adults absorb 5-10% of dietary lead
    Young children absorb 40-50% and retain 20-25%
  - Spontaneous excretion <50 ug/24 hr: may increase in acute poisoning
  - Absorption increased in diets
    - High in fat
    - Low in Ca, Mg, Fe, Zn, Cu
  - Distribution in two major compartments
    - Bone: Half life of 20 years
    - Soft tissues: Half life 20-30 days
  - Toxicity related to concentration in small, mobile soft tissue pool
**Distribution of Lead**

- Accumulates in two compartments
  - Labile that readily exchanges lead with blood
  - Inert pool
    - Mobilized during periods of stress e.g. pregnancy, lactation, fractures, chronic disease, anesthesia
    - Represents an endogenous source of lead- can maintain ↑ BLL long after exogenous source of lead removed.
- Lead toxicity may occur without a major acute exposure- lead accumulates over a lifetime and released slowly
“Acceptable” Blood Lead Level

- No “normal” lead level
- Lead not a normal element in body - serves no physiologic function
- “Acceptable” substituted for normal- reflects assimilation from food, water, and air
- “Acceptable” level in children by CDC criteria <5µg/dl; level periodically lowered as studies have shown adverse effects at previously acceptable levels
- Effects on enzymatic processes at levels as low as 5 µg/dl
  - Correct value for blood lead level should be 0
Neurobehavioral Effects of Lead

Noted at levels as low as 5 µg/dL
Correlated with dentine lead > 20 ppm

- Impairment of academic success –a 7-fold increase in failure to graduate from high school
- Lower class standing
- Greater absenteeism
- Impairment of reading skills (reading disabled)
- Deficits in vocabulary
  - Fine motor skills
  - Reaction time
  - Hand-eye coordination
Childhood Lead Exposure and Failure to Complete High School

Dentin Lead Quartiles (ppm) and Plumbism

Percent Failure

≤ 5.94
5.95-8.2
8.3-22.22
≥ 22.23

2/27
0/27
5/31
7/29

3/7

REPORTED PLUMBISM

X = 28.6 (7-52)

Seven children still in school are not included.

Childhood Lead Exposure and Reading Disability in Young Adulthood

Dentin Lead Quartiles (ppm) and Plumbism

*Reading disability defined as 2 or more grades below expected.

Pathophysiology of Cognitive Impairment

- In normal children, the brain synaptic density and complexity are markedly increased during the first two years of life
  - enzymes that mediate this process (including protein kinase C and calmodulin) are inhibited at very low concentrations of lead because of the replacement of calcium by lead in these enzymatic reactions
- Lead also impairs neural cell adhesion molecules and decreases neurotransmitter synthesis
  - result is reduced synaptogenesis and imprecise synaptic pruning
- Lead uncouples mitochondrial oxidative phosphorylation in the CNS
Developmental Neurotoxicity of Lead

- Port Pirie Cohort Study (1988 & 1992) showed effects of EBL on IQ with an average loss of 2 to 3 points for BLLs averaging 20 ug/dl, compared with BLLs averaging 10 ug/dl.

- Using research instruments that provide valid, reliable measures of attention, and behavior, investigators have identified associations between lead exposure and:
  - weaknesses in attention/vigilance (Bellinger; 1994)
  - aggression (Sciarillo; 1992)
  - somatic complaints
  - antisocial or delinquent behavior (Needleman; 1996)
Range of Toxic Effects of Lead

- Decreased stature
- Decreased hearing acuity
- Inability to maintain steady posture
- Impairment of biosynthesis of active vit D metabolite, 1,25- (OH)2 vit D
- Low total and ionized calcium levels
- Reduced gestational age and birth weight related to elevated maternal and cord BLL
- Reduced reproductive potential
Diagnosis of Lead Clinical Poisoning

- Most patients are asymptomatic
- Symptoms are subtle and non-specific
- Physical examination generally not abnormal unless patient has acute encephalopathy
- Lead poisoning or plumbism should be considered in the differential diagnosis of
  - Iron deficiency anemia
  - Seizures
  - Mental retardation
  - Severe behavioral disorders/ADD/ADHD
  - Colicky abdominal pain
  - Cerebral and abdominal crises of sickle cell
Diagnosis of lead Poisoning

- Usually diagnosed based on screening rather than clinical manifestations
  - fewer than 5% of those diagnosed with lead poisoning are based on clinical presentation

- The BLL is a “snapshot” in time, as lead does not remain in blood for long periods of time relative to its turnover in bone
  - low BLLs do not exclude the possibility of substantial bone lead stores
  - high BLLs do not necessarily signify a large body burden
Lead Poisoning in Children
Laboratory Evaluation

- Blood
  - Lead level
  - Erythrocyte protoporphyrin (EP)
  - Complete blood count (Hgb, RBC indices, WBC)
  - Peripheral blood smear (basophilic stippled RBCs)
  - Hemoglobin solubility
  - G6PD screen

- Urine
  - Urinalysis
  - Qualitative coproporphyrin
  - Lead output

- Radioimaging studies
  - Flat plate of abdomen
  - Long bones (wrists and knees)
Flat Plate of the Abdomen in a Child with Lead Poisoning

Radio-opacities (lead paint flecks or chips) in the ascending, transverse, and descending colon
X Ray of Long Bones in a Child with Lead Poisoning

Radio-opaque dense lines (lead lines) at the metaphyseal ends of femur and tibia
X Ray of Long Bones in a child with Lead Poisoning

Dense lines (lead lines) at the metaphyseal ends of radius and ulna
# Recommended Schedule for Obtaining a Confirmatory Venous Sample

<table>
<thead>
<tr>
<th>Blood µg/dl</th>
<th>Time to confirmation testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Reference Value-9</td>
<td>1 - 3 months</td>
</tr>
<tr>
<td>10-44</td>
<td>1 week - 1 month *</td>
</tr>
<tr>
<td>45-59</td>
<td>48 hours</td>
</tr>
<tr>
<td>60-69</td>
<td>24 hours</td>
</tr>
<tr>
<td>≥70</td>
<td>Urgently as emergency test</td>
</tr>
</tbody>
</table>

* The higher the BLL on the screening test, the more urgent the need for confirmatory testing.

(Adapted from: Screening Young Children for Lead Poisoning: Guidance for State and Local Public Health Officials. Atlanta: CDC; 1997.)
Blood Lead Level Interpretation

- Lower than 5 µg/dl
- 5-9 µg/dL
- Higher than 10 µg/dl
- Higher than 40 µg/dl
- ?Acceptable
- Level of concern
- Environmental evaluation, nutritional counselling, follow-up until resolved
- Chelation
Treatment of Lead Poisoning

I. Source Identification and Eradication
   A. Notify department of health for home inspection

   B. If household leaded paint is the source, deleading should be done by certified contractors so that lead dust is not disseminated throughout the house during repairs

   C. Recommend wet-dusting and -mopping with phosphate-containing detergent until definitive repairs are made and, also, on a continuing basis
Changes in PbB and FEP levels in an infant hospitalized with undue lead absorption subsequent to remaining in a home during burning, scraping, and sanding of lead-based paint. Infant underwent chelation therapy that reduced PbB from 65 to 22 µg/dL. The subsequent rise in PbB from 22 to 47 µg/dL indicated incomplete abatement of lead hazards. The family then moved to modern “lead-free” public housing, where PbB and FEP decreased after several weeks.

Adapted from Chisolm JJ Jr, Barltrop D: Recognition and management of children with increased lead absorption Arch Dis Childh. 1979;54:249-262.
Treatment of Lead Poisoning

II. Nutrition

A. Check for adequate iron and calcium intake

B. Iron supplementation, if iron deficiency present, even without anemia

C. Supplementation of other trace metals such as copper, zinc in the form of Multivitamin preps with minerals
Treatment of Lead Poisoning

III. Chelation Therapy

- Most clinicians will agree with chelation at $\geq 45 \, \mu\text{g/dl}$; most ineffective method of removing lead - only 2% of total body lead removed
- Patients should be evaluated for chelation on the basis of
  - clinical presentation
  - BLL and EP measurements
  - age
  - presence of iron deficiency
  - lead body burden
Chemical Structure of Chelating Agents for Treatment of Lead Poisoning

- Succimer (2,3-Dimercaptosuccinic acid)
- 2,3-Dimercaptopropanol (BAL)
- Calcium disodium EDTA
- d-Penicillamine
Pharmacologic effects due to formation of chelates with divalent and trivalent metals

Stable chelate formed with any metal that has the ability to displace calcium from the molecule, a feature shared by Pb, Zn, Cd, Mn, Fe, and Hg (excretion of Zn most increased)

In blood all the drug is found in plasma, does not penetrate cells, distributed primarily in the extracellular fluid with only 5% of the plasma conc found in the spinal fluid; excreted via the kidney
Clinical Pharmacology
BAL (Dimercaprol)

- Two molecules of BAL combine with one atom of heavy metal to form a stable complex
- Diffuses well into erythrocytes, enhances fecal and urinary excretion of lead
- Because predominantly excreted in bile, can be administered in presence of renal impairment
- Crosses the blood-brain barrier
Clinical Pharmacology

D-Penicillamine

- Specific mechanism and site of action are not well understood
- Enhances urinary excretion of lead
- Oral chelator
Clinical Pharmacology
Dimercaptosuccinic Acid (DMSA)(Succimer)

- Orally active, \textit{in vitro} forms stable water soluble complexes with lead
- Selectivity for lead is high, whereas ability to chelate essential trace metals is low
- Chemically similar to BAL but is more water soluble
Figure 2. Mean blood lead concentrations of children receiving succimer at approximately 10, 20, and 30 mg/kg/day and CaNa₂EDTA 1000 mg/m²/day for five days as a function of time (with permission).\textsuperscript{15}

Figure 3. Mean erythrocyte ALA-D activities measured as nanomoles of porphobilinogen per gram of hemoglobin per hour (nm PBG/g Hgb/hr) of children receiving oral succimer and intravenous CaNa₂EDTA 1000 mg/m²/day as a function of time.\textsuperscript{15,16}
Comparison Between BAL/EDTA and DMSA/EDTA

Figure. Relation between BPb and day of treatment or days after chelation. Vertical bars represent Sds. Significance values: (no symbol), p >0.6 for day 14 versus day 33 BPb in each group; +, p <0.02 compared with pretreatment values; *, p <0.01 compared with pretreatment values; **, p <0.001 compared with pretreatment values.

DMSA (2,3-Dimercaptosuccinic Acid) Succimer (An Analog of Dimercaprol)

- An oral chelator, recently approved for use in children with blood lead levels higher than 45 µg/dL
- A 19-day course is recommended; the first 5 days consists of a three-times-a-day regimen followed by 14 days at two-times-a-day
- Transient elevations in transaminases, WBC and platelet count, rash, and abdominal upset are frequent
- Less of the essential minerals are lost during chelation (as compared to Ca Na₂ EDTA)
Concerns Regarding Use of DMSA

- Treatment should be given in a controlled, lead-free environment; consequences of eating lead and receiving DMSA at the same time are unknown and not studied adequately in children.
  Treating children as outpatients without removing them from the lead source may be potentially harmful.

- Data regarding use in children is still scanty; less common side effects may still not have been identified; so direct observation for toxicity may be prudent.
Concerns Regarding Use of DMSA (contd)

- It is likely, initiation of treatment disturbs equilibrium and causes shifts of lead within compartments. If parents not compliant with regimen (which may be very possible) and miss doses, lead content in sensitive organs such as the brain may increase as lead is chelated from bone and no chelating agent is available to bind it
Chelation Therapy at Children’s Hospital of Michigan

- CDC and the Committee on Drugs of the AAP recommend chelation in children with monotherapy consisting of either parenteral CaDisodiumEDTA or orally administered DMSA with BLL 45-69 µg/dL
- In spite of above recommendations, goals of chelation therapy (except for the prevention of lead encephalopathy) have not been defined in asymptomatic children
- In light of information suggesting neurotoxicity is dose related, our goal of inpatient chelation is to maximize lead elimination
- Consider the child’s age, other evidence of tissue toxicity i.e. EP level, and presence of iron deficiency in decision-making for inpatient chelation
Chelation Therapy at CHM

- Inpatient: Aggressive Management
  - BAL and Ca Disodium EDTA parenterally for 5 days for BLL > 70 µg/dL
  - Ca Disodium EDTA IV and oral DMSA for 5 days for BLL ≥ 40 µg/dL
Treatment of Lead Poisoning

- Follow-up should be individualized and the child followed until 6 yr of age or longer, if necessary.
- Serial measurements of BLL and EP for evaluation and monitoring.