Training Manual on Pediatric Environmental Health: Putting It Into Practice

Children's Environmental Health Network
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Childhood Lead Toxicity

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This module addresses the toxicology of lead with specific emphasis on the risks this metal poses to children. The module is designed in a lecture format with suggested learning exercises built around case studies. Accompanying tables and materials may be used for slides or overhead projections. (For a discussion of the health risks of other heavy metals, consult the module "Metal Toxicity in Children.")

Learning Objectives

After completing this module, faculty will be able to teach students and residents to develop a basic understanding of:

- common sources of exposure to lead
- common routes of poisoning
- the biochemical, subclinical, and clinical effects of lead poisoning
- the main components of the diagnosis and treatment of childhood lead poisoning

General Principles of Lead Toxicity

Case Study

Every pediatric provider should be able to recognize the clinical signs of lead poisoning. The following vignette is an example of how such a case might present in your practice.

A 2-year-old female came into the emergency room with a three-week history of intermittent abdominal pain, loss of appetite, vomiting, constipation, and increasing apathy. One week prior she had been seen in her pediatrician's office with the same complaints. An evaluation found that the child resided in an old house with peeling paint. The pediatrician had reassured the mother that the child was probably suffering from intestinal flu, but did obtain a blood sample that was sent to a commercial lab for analysis. There were no focal or abnormal findings on physical examination in the ER, with the exception of a pulse of 140 and a lethargic but awake child who would not cooperate with the examiner. Within a few minutes of evaluation, the child developed major motor seizures and suffered a cardiopulmonary arrest. She was intubated and successfully resuscitated. At that point the ER physician called the lab and determined that a lead level had been ordered by the pediatrician the week before. The sample had been processed on the day the pediatrician ordered it; results indicated a lead level >200 μg/dL. Neither the child's pediatrician nor the laboratory had followed through on the results of the ordered test. Chelation and supportive therapy were begun.

Characteristics of Lead

Lead (Pb) has an atomic number of 82, an average atomic weight of 207, and a melting point of 327° C. At room temperature, it is a white soft metal. Lead can be found in oxidation states 0, +2 and +4, but it is the +2 form that is of biological concern. Although organic lead compounds (tetraethyl lead) have been used as gasoline additives, inorganic lead compounds are the species of current concern.

Sources and Uses of Lead

Lead in paint is the most common source of environmental exposure. Because lead makes paint more durable, the metal was, for many decades, routinely used as an additive. Although its detrimental health effects were recognized early in the twentieth century, it was not until 1976 that use of lead in paint was legally limited to formulations intended for marine use or for areas prone to excessive weathering, such as bridges. However, leaded paint from the old formulation remains in an estimated 25-40 million U.S. homes.

In addition to its restricted paint uses, lead is currently used in vehicular batteries, cable sheathing, chemicals, and many construction materials. The permissible amount of lead in gasoline produced for use in the United States was reduced by 90% a decade ago, to 0.1 μg/L. Meanwhile, leaded gasoline continues to be used in much of the developing world. Lead has also been found to be a component of several cosmetics and folk remedies in use in Latin America, the Mideast, and Asia. Travelers from these areas may bring these sources with them when they visit or immigrate to the United States.

Routes of Delivery

The gastrointestinal tract serves as the primary route of entry into the body. Lead fumes may be inhaled, resulting in the absorption of very small particles through the lung. Hand-to-mouth behavior can result in ingestion of lead-containing dust or paint chips. Children may also drink contaminated water or swallow phlegm contaminated with inhaled lead. Organic lead can be absorbed transcutaneously but inorganic lead, the type found in paint, is poorly absorbed through the skin.

Susceptibility

The occurance of lead poisoning depends on the developmental stage, behavior, nutritional status, and metabolism of an exposed individual. The exercise on the following page reviews some of the different factors affecting a child's susceptibility.

Exercise: Ask residents or students to imagine a class of three-year-old children in a Head Start program. The children and teachers are situated in a dilapidated classroom in a building constructed before 1960. Only a few of these children will have elevated blood lead levels or lead toxicity as a consequence of this exposure. Why?

Review the following possibilities with your students or residents:

- The children can be divided into two groups on the basis of their behavior. Those engaging in pica or hand-to-mouth activity, such as finger-sucking, are more likely to ingest lead.
- The children can be divided into two groups on the basis of their nutrition. Some of the exposed children may have drunk milk at home or at school. Calcium in the milk will compete with lead for absorptive sites. Thus, the exposed children who suffer from poor nutrition are more likely to have elevated blood lead levels.
- The children can be divided into two groups based on genetic traits. In the group with elevated blood lead levels, only some of the children will have evidence of lead toxicity. These children may have inherited a genetic trait that makes the function of specific enzymes particularly sensitive to lead.
- The adults in the room will be less likely to have elevated lead levels or to experience toxic effects because their developmental status reduces their risk. They are less likely to engage in behavior that places them at risk for lead ingestion, and their organ systems are less vulnerable to comparable amounts of lead.

Effects of Lead on the Body

Biochemical

Lead exerts its effects through several biochemical mechanisms. The diversity of these mechanisms is such that virtually all cells are affected by this metal.

- *Lead has a high affinity for many calcium-binding proteins (e.g., calmodulin, troponin).* Once bound to such molecules, it may activate or inhibit processes that are normally calcium-mediated, thus disrupting normal intracellular calcium-relayed messages. Lead may also affect neurotransmitter release, distorting intercellular communication.

- *Lead can adversely affect enzyme function.* Lead has an affinity for sulfhydryl and amide groups, and it can bind to enzymes that contain those groups, altering their configuration and diminishing their activities.

The relationship between lead and enzymes of the heme pathway, which is found in all cells, has been well studied. At least three of the seven enzymes in this pathway are poisoned by lead, resulting in diminished production of heme and in the buildup

of substrate. Because these substrates may be toxic when present in excessive amounts, the detrimental effects of lead may be multiplied by the presence of abnormally high levels of normal biochemical constituents of the cell.

Increased erythrocyte levels of the heme precursor protoporphyrin (EP) are used as a marker of lead toxicity; EP levels greater than 35 μg/dL are associated with lead levels greater than 25-50 μg/dL. There is, however, a delay of several weeks between the beginning of lead exposure and its accumulation in the body and consequent rise in EP levels.

Another heme pathway enzyme affected by lead is ALA dehydratase. ALA dehydratase activity and susceptibility to inhibition by lead varies between individuals and is transmitted as an autosomal genetic trait. Blood lead concentrations as low as 15 μg/dL inhibit this enzyme in susceptible children. Of interest is the observation that reduction of blood lead levels by treatment is associated with an immediate reversal of this toxic effect. Thus, ALA-dehydratase activity can be used longitudinally as a marker of the success of treatment.

Subclinical

Epidemiological studies conducted in the U.S. population have shown subclinical effects in both height and hearing in children with blood lead levels in the range of 0-40 μg/dL. As blood lead increases by 10 μg/dL, children are, on average, about 1 cm shorter than the genetic potential would otherwise predict. It should be emphasized that this is a subclinical finding; the effect is not large enough to bring the average child to the endocrinologist for evaluation of short stature. Similarly, hearing at all frequencies decreases as blood lead levels increase. Again, this is a subclinical finding. Typically there is no complaint of deafness from the parents of a mild/moderately lead-poisoned child. Rather, parents describe a child who won't listen.

Perhaps the most critical subclinical effects of lead poisoning are observed in the cognition and behavior of children. The effect on cognition is most pronounced when exposures occur *in utero* or in the first years of life.

- Prenatal lead exposure resulting in cord blood lead levels as low as 15 μg/dL has been associated with an average 6-point decrement in the Mental Development Index on the Bayley Mental Development Scale, when compared to infants born with cord blood lead levels of 2 μg/dL. This difference in scores persisted for the first two years of life and was independent of concurrent blood lead measurements.

In addition, the blood lead level at approximately two years of age has been shown to correlate with future results on cognitive testing performed 2-8 years later. The magnitude of the relationship has varied between studies but averages about 0.5 (i.e., for every 1 μg/dL increase in the blood lead level at age 2 years, the cognitive test score is reduced by 0.5 units). The lag between time of elevation in blood lead levels and time of adverse impact on cognitive test results is noteworthy. In longitudinal studies, blood lead levels measured at the time of cognitive testing (ages 2, 5, 7, or 10 years) did not correlate with results of intelligence tests, such as the Bayley or McCarthy Scales of Children's Abilities.

- Behavior also appears to be detrimentally affected by lead. Previous studies found teacher ratings of behavior to be poorer in children with higher tooth-lead levels. A recent study of 7- to 11-year-old children found a significant relationship between bone lead levels (measured by x-ray fluorescence) and behaviors predictive of later delinquency (Needleman, 1993).

Clinical

Symptoms and signs related to specific organ systems — particularly the gastrointestinal tract and central nervous system — are found in children with elevated blood lead levels. The clinical symptoms of lead poisoning, however, are found in less than 1% of all children with blood lead levels of 10 μg/dL or higher, and generally become apparent only late in the progression of the disorder.

- When blood lead concentrations reach 50 μg/dL or higher, patients often complain of gastrointestinal symptoms such as pain, loss of appetite, nausea, vomiting, and constipation. These symptoms often go unrecognized for weeks.
- Central nervous system symptoms are also common. Parents often complain of hyperactivity in children with even mildly elevated blood lead levels (over 10 μg/dL). The threshold for this effect is unknown. At very high levels, generally greater than 100 μg/dL, children may exhibit signs of increased intracranial pressure and develop seizures or lapse into a coma (encephalopathy). In contrast to adults, lead-poisoned children rarely show peripheral nervous system effects, but wrist and foot drop may, on a rare basis, occur.

Diagnosis

A three-pronged approach is needed to diagnose clinical symptoms of lead poisoning:

- an age-appropriate medical history that identifies the presence of risk factors, such as known exposure to peeling leaded paint and pica behavior;
- a careful evaluation of GI and CNS clinical symptoms; and
- a tissue sample for direct lead determination.

Screening

The current gold standard for determining whether lead absorption has occurred is a measurement of the blood lead level. Blood lead has been chosen because, as the body's highway for the distribution of this metal, it reflects the confluence of absorption, entry to and from soft and hard tissue stores, and renal filtration. Of the methods currently available for detecting lead absorption, it is also the easiest to perform. A blood lead level >10 μg/dL is considered elevated (CDC, 1991).

Until 1997, the CDC recommended universal screening of all preschool children using this method. Subsequently, given the fall in prevalence of lead poisoning, the CDC revised its guidelines. Blood lead screening is now based on local risk assessment of exposure to lead. It is up to state and local health departments to determine the level of risk and to issue policy guidelines for providers. In the absence of formal local guidance, "universal screening should be carried out" (CDC,1997). This means that all children should be screened by blood lead measurement at 12 and 24 months of age,

and at 36-72 months of age if not previously screened. Where local risk has been defined and found to be low, targeted screening may suffice. Minimum Personal Risk Questionnaires (see table below from CDC, 1997) may be used as a first-pass screening method, followed by blood lead testing if the answers indicate high risk.

Overall, the sensitivity of questionnaires designed to identify lead-poisoned children is about 60-70%. Sensitivity can be improved when local conditions are considered and locally appropriate questions are added.

Exercise: Students and residents can develop additional personal risk questions to reflect local conditions. For instance, adding the question, "Does the child live near an industrial site that uses lead, such as a battery factory or a smelter?" may improve the sensitivity of the questionnaire.

Minimum Personal Risk Questionnaire

1. Does the child reside in or regularly visit a house that was built before 1950? (Include settings such as daycare, and a babysitter, or relative's home)
2. Does the child reside in or regularly visit a house built before 1978 undergoing recent (past 6 months) or current renovation?
3. Does the child have a sibling or playmate who has been diagnosed with lead poisoning?

Alternatively, selection for blood lead testing may be based on residence in a geographic area known to have large amounts of lead or on membership in a high-risk group, such as indigent children.

Follow-Up

If initial blood testing finds the child's blood lead level to be >10 µg/dL, then careful follow-up is mandatory. The following table, derived from the 1997 CDC statement "Screening Young Children for Lead Poisoning" summarizes the timing of follow-up to the screening test.

If screening blood lead level (µg/dL) is:	Repeat diagnostic venous blood lead testing:
10-19	in 3 months
20-44	in 1 month – 1 week (the sooner the higher the lead)
45-59	in 48 hours
60-69	in 24 hours
>70	immediately

If the diagnostic screening test confirms an elevated blood lead level, then the following is recommended:

Diagnostic blood lead level (μg/dL):	Action:
10 – 4	Repeat within 3 months
15 – 19	Repeat within 3 months
15 – 19 x2; or ≥20	Clinical management: take medical, nutritional and environmental history; perform physical exam; arrange environmental inspection; consider possible chelation therapy

Other methods of assessment

The blood concentration of a metal is not fully predictive of the amount of the metal in a critical organ such as the brain, and symptoms for a given blood lead level may vary greatly among individuals. Other methods are available to assess the presence of lead in the body.

Measuring lead in urine:

Spontaneous excretion of lead in the urine, even in markedly lead-poisoned children, may not reach very high levels. However, (6-8 hours) after the administration of a dose of the chelating agent calcium disodium edetate ($CaNa_2EDTA$), a large increase in urinary lead content will be noted in some children with moderately elevated blood lead levels of 25-44 μg/dL.

This drug-induced urinary lead excretion has been correlated with bone lead content as well as blood lead levels; the higher the blood or bone lead, the more likely a large lead diuresis will be induced by the drug. It may therefore reflect body stores of lead as well as a fraction of that lead which is mobile, i.e., not bound in the deep crystalline compartment of bone, and hence, potentially more likely to produce toxic effects.

Use of $CaNa_2EDTA$ as a diagnostic agent has been formalized in the Lead Mobilization Test (LMT). The test consists of the administration of a standard dose of $CaNa_2EDTA$ (e.g. 500 mg/m^2 once, given IM or IV; if IM it is first mixed 1:1 by volume with 1% procaine), followed by a timed (6-8 hour) urine collection for Pb content determination. If the response to the drug is a large Pb excretion, then a full course of chelation is immediately begun. It is likely that children selected for chelation on the basis of this test will excrete considerably more lead during the course of treatment then they would have excreted spontaneously, that their blood lead levels will decline, and that enzyme function will improve in the short-term. It has not, however, been determined whether chelating children on the basis of a positive LMT alters the long-term course of their disease. Although performed successfully at some clinical centers, the LMT is not currently recommended by the American Academy of Pediatrics as part of the evaluation process of lead -poisoned children.

Measuring lead in bone:

Although 70-95% of the body content of lead is found in the skeleton, obtaining a piece of bone for lead determination is not practical. Direct, non-invasive measurement of bone lead content, however, is now feasible with x-ray fluorescence technology. Instruments use a low-dose radiation beam, aimed at a particular bone — such as the tibia — to excite any lead atoms that are present to fluoresce. The photons emitted from the bone are counted and a quantitative estimate of the bone lead content is thus obtained. Unfortunately, few such instruments are available nationally and their use is generally restricted to clinical research.

Treatment

There are four components to the treatment of lead poisoning: environmental control, behavior modification, nutrition counseling, and chelation therapy.

Environmental control

The most important action is to eliminate the source of lead exposure, thereby inhibiting further poisoning. Since leaded paint is the most common source of environmental exposure, the child should not be allowed access to areas with flaking, lead-based paint until these surfaces are repaired and the lead-containing paint removed. Abatement procedures should be carefully performed; otherwise, leaded dust can be disseminated throughout the home and local neighborhood, increasing the health risk to occupants. Once removal of the lead-containing paint is complete, ongoing clean-up with a lead-binding detergent and a high efficiency particle air (HEPA) vacuum is essential.

Behavior modification

Since lead must find some way of entry into the body in order to cause health problems, behavioral modification directed toward both parent and child may be helpful. The parent should be instructed to clean dust and loose paint from surfaces before and after abatement procedures, as described in the preceding section. The parent should also closely observe the child in order to inhibit the hand-to-mouth activity that accounts for most ingestion of lead. Washing the child's hands before eating will also help to remove surface lead before it can be ingested.

Nutrition counseling

Nutrition influences the amount of lead absorbed by the intestine as well as the effects of this metal on the body. A diet deficient in calcium and iron may enhance lead absorption, retention, and toxicity. Therefore, the clinician should determine the child's daily intake of these elements and correct deficiencies either by dietary modification or with mineral supplements. It has been suggested that other dietary components, such as fat intake, may affect lead absorption, but little data exists to support these contentions.

Chelation therapy

Chelation therapy is the use of drugs to bind lead and enhance its excretion. The CDC currently advises chelation for children with blood lead levels of 45 μg/dL or

greater. Four drugs are now available for chelation. Two of these can be given orally: succimer (DMSA, Chemet) and penicillamine (PCA, Cuprimine). Of these oral agents, only succimer is FDA-approved for the treatment of lead-poisoned children with levels >45 μg/dL. The other two drugs must be administered parenterally: calcium disodium edetate (CaNa2EDTA), given IV or IM; and BAL (Dimercaprol), given IM.

Each of these medicines has its own toxicity profile, but serious adverse effects are rare and generally reversible. Side effects, such as rashes and blood dyscrasias, are of greatest concern with penicillamine use, but generally they can generally be minimized when the drug is administered by a knowledgeable practitioner.

The long-term efficacy of chelation therapy for any group of asymptomatic lead-poisoned children has yet to be fully evaluated. However, the well-defined subclinical and biochemical toxicity induced by lead in children with elevated blood levels <45 μg/dL, and the metal's potential for causing permanent cognitive deficits, have prompted some experts to chelate moderately lead-poisoned children (blood lead 20-45 μg/dL). This response is determined either on the basis of blood lead levels alone, or in conjunction with the results of other diagnostic tests, such as the Lead Mobilization Test (LMT). Children who undergo the LMT and have a large lead excretion are treated immediately with a full course of chelation, as indicated earlier.

Blood lead levels fall rapidly but temporarily with chelation therapy. Most children exhibit a rebound in their blood lead levels within days to weeks of completion of treatment. Levels eventually stabilize somewhere between the pretreatment peak and immediate post-treatment trough. Without chelation treatment, but with cessation of ingestion, blood lead levels will also eventually fall as a function of aging in most children. Presumably, this fall in blood lead levels reflects a declining lead content in critical organs, and reduced toxicity. Active treatment (with or without chelation) over three to six months is associated with a fall in blood and bone lead measures and an improvement in cognitive scores and behavior (Ruff, 1993).

Learning Methods

This material is best suited for lecture format with interactive questions. It may be used for Grand Rounds presentations.

Evaluation Methods

Increased awareness of the potential sources of lead poisoning should be reflected in the medical records. Chart reviews may determine whether parents and children have been asked age-appropriate questions on possible exposures to lead, and whether blood lead screening has been performed.

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