Putting it into Practice: Pediatric Environmental Health Training Resource

Childhood Lead Poisoning

User Guide

Children's Environmental Health Network

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I. Notes on slides

Slides 6-10

The major point about sources/pathways of lead exposure is that there are a multitude of ways in which child are exposed to lead. Deteriorated lead-based paint is the most likely source for children with a very high blood lead level (i.e., >30 g/dL), and the older the home, the higher the likelihood that it contains a lead hazard. However, it might be that no single source/pathway can be identified as being of paramount importance for an individual child who has a blood lead level lower than this. Lead in dust, water, food, folk/complementary medicines, cosmetics, etc., might all contribute. Many studies, however, do report that, on a group basis, lead in house dust is one of the most important contributors to children's blood lead levels due to children's hand-to-mouth activities.

A thorough environmental history, using questions such as those listed on slides 46-50, should be taken as a particular child's elevated blood lead level could be the result of a circumstance that is relatively uncommon.

Slide 11

This slide depicts aspects of the kinetics of lead in the body. Following exposure by either ingestion or inhalation, lead makes its way into blood, with 95% bound to the membranes of red cells. The remainder is unbound in the blood plasma, which is thought to be the fraction that is most toxic. The efficiency of absorption is perhaps slightly greater for inhaled than for ingested lead. Children are thought to absorb a greater percentage of ingested lead than are adults, and absorption increases with fasting and with certain dietary conditions, most notably iron or calcium deficiency. The half-life of lead in blood is considered to be about 30 days, but the kinetics are such that lead moves back and forth between its major pools in the body. Besides the blood, lead finds its way to soft tissues and hard tissues, such as bone. In an adult, approximately 90% of the total body burden of lead is in bone, with a half-life that is measured in decades (longer in dense cortical bone than in spongy trabecular bone). In children, only about 70% of the total body lead burden is in bone, and it appears to move in and out of bone freely during the rapid bone remodeling that occurs during childhood. Some studies show that bone lead levels are not elevated in adolescents known to have been clinically lead-poisoned as young children.

Slide 12

This slide provides a general idea of the adverse effects evident in different organ systems at different blood lead levels in children. Adverse developmental effects are consistently observed at blood lead levels below the former CDC "level of concern" of 10 µg/dL. This concept has been abandoned by the CDC (as of 2012) because of the absence of evidence that ANY level of

lead is safe in children. It should not, perhaps, be surprising that a blood lead level that is only 10% of a potentially fatal dose would impair health, yet, until the 1970's, a blood lead level that was approximately half of the potentially fatal dose was accepted as "normal."

Slide 13

This is a list of the processes involved in brain development and function that have been shown to be associated with lead exposure. They are dose-dependent and some, such as increased apoptosis (programmed death of neurons) and excitotoxicity, likely occur only at rather high dose. Lead's effect on neurotransmission (cell-cell signaling) is likely to be an important mechanism of low-level neurotoxicity. In the adult CNS, neurotransmitters largely serve to mediate cell-to-cell transmission of action potentials. This is also true in the immature CNS, but. In addition, they serve as morphogenetic signals that contribute to the fine structure, the establishment and distribution of different neurotransmitter systems. In addition, there is an initial exuberance of synapses which undergo systematic elimination or "pruning" during postnatal development, extending into adolescence. The selection of the synapses to be retained is activity-dependent such that it is the synapses that are most frequently active that tend to survive. Lead is thought to disrupt the signal transduction function of the neurotrophic factors that regulate this selection process. It both inhibits the stimulated release of neurotransmitter into the synaptic cleft and increases the unstimulated release of neurotransmitter, introducing "noise" into this process, likely placing at a competitive disadvantage synapses that should be the ones to survive.

Slides 15-17

These slides provide neuroimaging findings from the Cincinnati Prospective lead study. A birth cohort of children was enrolled during pregnancy and followed up for more than two decades. Detailed data were collected on each child's blood lead history, neurodevelopment, and on potential confounders. It should be noted that these children were primarily poor minorities from the inner-city, with blood lead levels that were typical for the 1980's but high compared to contemporary levels (e.g., mean biannual blood lead level to age 6.5 years was 8.3 µg/dL, range 2-34). When the children reached 19-24 years of age, morphometric MRI, diffusion tensor imaging, magnetic resonance spectroscopy (MRS), and functional MRI studies were conducted. Slide 15 shows the areas in which children with higher blood lead levels in childhood showed significant volume loss. As indicated, most prominent among these areas was the prefrontal cortex. (This is most easily seen in the two mid-sagittal slices at the top). This is an area of the brain that has been implicated in many of the neurodevelopmental impairments that have been associated with increased lead exposure. Slide 16 shows that higher childhood blood lead levels were associated in this cohort with evidence of white matter disorganization, suggesting disordered myelination and compromised axonal integrity. In Slide 17, the results of MRS suggested that higher childhood blood lead levels were associated with changes in metabolite ratios, in both grey and white matter, that are considered to be evidence of brain dysfunction. In another study (not shown), during a verb generation task, adults with higher blood lead levels in early-life showed altered activation patterns in the "language-speech areas" of Broca (left frontal) and Wernicke (posterior region of superior temporal gyrus)(Yuan et al., 2006).

Slide 18

Many risk assessment groups have concluded that developmental neurotoxicity is the most sensitive endpoint for childhood lead poisoning. This slide indicates that a clear "behavioral signature injury" (i.e., a constellation of neurodevelopmental impairments that is unique to lead and could be used to identify a child with higher exposure) has not been identified. Instead, adverse effects have been noted on a wide range of cognitive and behavioral domains that can vary from study to study. The basis for this variability is not clear, but it likely reflects the influence of many factors on the expression of lead neurotoxicity, including characteristics of the exposure (e.g., age at exposure, co-exposures to other neurotoxicants), age at assessment, genetics, social context (e.g., socioeconomic status, nutrition), etc. This implies that the only way to identify a child with higher exposure is to measure his or her blood lead level.

Slides 19-20

The strongest evidence available regarding the relationship for blood lead and children's neurodevelopment (specifically Full-Scale IQ) comes from a pooled analysis of 1,333 children enrolled in 7 prospective studies conducted in North America, Europe, and Australia (Lanphear et al., 2005). Blood lead levels in childhood, near the time of IQ assessment, were most strongly related to IQ, although blood lead levels measured at some other times were also associated with IQ. The dose-effect relationship was estimated over the range of 2.4 to 30 µg/dL. (Data were sparse below or above this range). A variety of statistical models were compared, with log-linear and restricted spline models both suggesting that the dose-effect relationship is not linear but supra-linear. Specifically, the decline in Full-Scale IQ over the range of blood lead levels from 2.4 to 10 µg/dL (3.9 points) was greater than it was over the range of 10-20 µg/dL (1.9 points) or 20-30 µg/dL (1.1 points). A biological explanation for this dose-dependent rate of change has not been found, but supra-linearity in the dose-effect relationship between blood lead and neurodevelopment has since been reported independently in several other studies.

Slides 21-22

Because some question that practical importance of a loss of a few IQ points, it is important to point out that many studies show that children with higher blood lead levels also perform poorly on tests of academic skills such as reading and mathematics. Slide 21 shows that children with concurrent blood lead levels between 5 and 10 µg/dL scored significantly lower on both reading and math even when adjustment was made for IQ. In other words, among children with the same IQ score, those who were more highly exposed performed worse than children who were less exposed to lead. This demonstrates that lead produces a discrepancy between aptitude and ability, such that more highly exposed children do not learn at the rate that would be expected based on their IQ scores. Slide 22 shows the results of a study which combined statewide databases of children's blood lead levels and performance on a reading test administered at the end of 4th grade (North Carolina). The slide shows a clear dose-response relationship between blood lead level (range of 1-≥10 µg/dL) and the percentage of children who failed to achieve a passing grade on this test. Specifically, the rate of failure increased from about 10% among children with a blood lead level of 1, to more than 30% among children with a blood lead level greater than 10 µg/dL.

Slide 23

Childhood lead exposure has been linked to an increased risk of several behavior disorders, with ADHD (Attention Deficit Hyperactivity Disorder) being the one that has received the most research attention. Using NHANES 1999-2002 data, Braun et al. (2006) identified 6-15 year old children who, by parent report, had been diagnosed with ADHD by a health professional and who were taking ADHD medicine. Adjusting for several covariates (though not family history of ADHD), a dose-response relationship was observed such that the odds ratio associated with a blood lead level greater than 2 μg/dL was approximately 4 (using children with a blood lead level <0.8 μg/dL as the reference group). The odds ratios associated with the three intermediate categories (0.8-1.0, 1.1-1.3, 1.4-2.0) rose monotonically. Many previous cohort studies had shown that more highly exposed children tended to display more behaviors associated with ADHD (e.g., distractibility, impulsivity) but the Braun et al. (2006) study was one of the first to extend the link to the ADHD diagnosis.

Slide 24

Several cross-sectional or case-control studies have reported an association between lead and social pathology, including aggression, anti-social behavior, conduct disorder, and delinquency. The most rigorous evidence relevant to this association has come from the Cincinnati Prospective lead study. Wright et al. (2008) accessed the county criminal justice records of Hamilton County in Ohio, where the individuals enrolled in the cohort resided to determine the number of times each participant had been arrested. For both total arrests and arrests specifically for violent crimes, with each 5 μg/dL increase in blood lead during various intervals (prenatal period, average childhood blood lead level, blood lead level at age 6 years) was associated with a 7-48% increase in the risk of being arrested. The strengths of this study include the use of administrative records rather than self- or parent-report of the outcome and the prospective collection (prior to outcome measurement) of data on exposure and covariates.

Slide 25

This slide shows a simple chain by which increased childhood lead exposure might be linked to a variety of adverse outcomes. It is well-established that lead exposure is associated with reduced IQ and executive dysfunction (poor planning, organizing, and strategizing, poor impulse control, poor persistence, difficulty delaying gratification, etc.). It is hypothesized that as a child gets older these neuropsychological deficits place a child at increased risk of failing to achieve success in school, ADHD, conduct disorder, violence, substance abuse, and injury. In other words, it is not necessary to postulate a direct effect of lead exposure on these downstream outcomes. Rather they can be seen as eventual expressions of lead neurotoxicity that unfold over time as the result of interactions between the children's neuropsychological injuries and the increasing school, social, and vocational demands placed on them.

Slide 26

A recent finding that is very intriguing, at this point demonstrated only in rodents and non-human primates, is that early life lead exposure initiates a process by which patterns of gene expression in adulthood are altered, increasing the risk of Alzheimer's-like pathology (i.e.,

amyloid plaques) in the frontal cortex. (As noted earlier, this appears to be an area in which greater volume loss is seen among adults with greater childhood lead exposure, and ADHD is thought to reflect executive function deficits as a result of damage to this region). In a study of monkeys, early lead exposure was associated with increased mRNA expression of amyloid precursor protein, greater staining of amyloid beta, and reduced expression of DNA methyltransferase. One small study has been reported in humans (Mazumdar et al. Environ Health Perspect 2012;120:702-7), suggesting that an umbilical cord blood lead level ≥10 µg/dL may influence Aβ-related biological pathways that have been implicated in the onset of Alzheimer's Disease. It is very difficult to find a cohort for which measurements of prenatal lead exposure are available in order to explore hypothesis more fully in humans.

Slide 27

Data from prospective studies provide little indication that the neurodevelopmental deficits of more highly exposed children are remediated if later exposure is reduced, whether in the natural setting or by chelation therapy. The only randomized clinical trial of chelation (oral DMSA) ever conducted indicated that the neurodevelopmental outcomes were equivalent among children who received DMSA and those who did not. These findings clearly indicate that primary prevention of exposure should be the first-line strategy for preventing lead-associated neurodevelopmental impairments.

Slide 28

There are some provocative findings that suggest potential avenues for secondary prevention. Epidemiological studies provide some evidence that the context in which a child is exposed to lead affects the likelihood that neurotoxicity will be expressed, its severity, or its persistence, but it is animal studies that can provide the most rigorous assessment of this hypothesis. Guilarte et al. (2003) exposed half of the rat pups in their study to lead from conception through weaning and the other half to placebo. Half of the pups in each exposure group were raised in standard laboratory cages while the other half were raised in an "enriched" environment, which was larger, contained other rats to interact with, and included materials for climbing and exploring. In adulthood, the rats' ability to solve a spatial learning task (water maze) was tested over 4 days. The performance of the lead-exposed rats raised in an enriched environment was similar to that of the placebo rats raised in an enriched environment and superior to the performance of placebo rats raised in a standard cage. The lead-exposed rats raised in a standard cage failed to demonstrate any learning of the task. Thus, being raised in an enriched environment prevented the lead-exposed rats from manifesting the learning deficit that was evident among the lead-exposed animals raised in a standard cage. Moreover, the investigators also demonstrated that enrichment ameliorated biochemical deficits in the hippocampus of lead-exposed animals (specifically involving the expression of genes relating to the N-methyl-D-aspartate receptor and brain-derived neurotrophic factor).

Slides 29-33

These five slides provide information about the recommendations of the CDC and AAP regarding the screening of children and pregnant women for lead. The CDC and AAP recommendations for children both acknowledge the importance of applying practices that are

region-specific due to differences in the age of housing stock, background rate of elevated blood lead levels in children, the presence of certain subgroups at particular risk, etc. Practitioners should be familiar with the local guidelines for their region, with might involve targeted screening for certain groups considered to be at increased risk. Many studies have found that immigrant, refugee, and internationally adopted children are one such group and warrant increased surveillance. In 2010, the CDC recommended that blood lead screening be conducted among pregnant and lactating women among those identified by history as being at increased risk, and that 5 µg/dL be considered the level warranting follow-up testing, including testing of the blood lead levels of their offspring.

Slides 34-37

There is tremendous variability among children in terms of the signs and symptoms they display at a given blood lead level. It has been reported that some children with a level in the hundreds of micrograms/deciliter are asymptomatic. The bases for this variability are unknown. The major point is that children with a blood lead level that is associated with permanent cognitive deficit might be completely asymptomatic or show signs and symptoms that are nonspecific and might be attributed to many other causes. Slide 36 identifies other conditions that should be considered in the differential diagnosis. Slide 37 identifies some neurodevelopmental disorders for which excessive lead exposure should be considered as potentially contributory.

The next series of slides pertain to the medical management of children with elevated blood lead levels.

Slide 38

For most children, a physical examination is unlikely to produce any finding that would bear on the management plan, although it might be useful in identifying children for whom a referral for management of a neurodevelopmental disorder is indicated.

Slide 39

A diagnosis of lead poisoning is generally based solely on a child's blood lead level, as other clinical indicators are likely to be in the normal range. The potential usefulness of an abdominal film is that it might identify the likely source of a child's exposure (e.g., if paint chips are apparent or a lead-containing foreign object such as a fishing weight).

Slide 40

A variety of signs, biomarkers, and procedures that are sometimes touted as helpful in diagnosing lead poisoning should not be used.

Slide 41

The diagnosis of lead poisoning should be made on the basis of a venous blood sample rather than a capillary sample. An elevated blood lead level on capillary sample should be confirmed on a venous sample, with the urgency directly dependent on the capillary value.

Slide 42
Similarly, the interval between blood lead tests should vary depending on a child's venous blood lead level and on the temporal pattern of the levels.

Slide 43
There are several possible explanations for why a child's blood lead level might appear to increase over time, including simply laboratory imprecision, but also a new or hitherto-unrecognized source/pathway of exposure, the improper conduct of abatement activities that cause increased exposure, or incomplete abatement of a previously recognized source/pathway. Investigation should be undertaken to identify the cause so that an appropriate response can be mounted.

Slides 44-45
Treatment of lead poisoning involves four elements, the first of which is environmental control. This involves efforts to identify and then reduce or interrupt relevant sources/pathways of exposure. Because of the previously noted myriad of potential sources/pathways of exposure, to do so requires a careful environmental history (example questions on Slides 46-50) focusing on the child's residence, neighborhood, behavior, and family characteristics and practices.

The next two components of treatment are educating parents about ways to reduce their child's exposure, including the importance of cleaning and hand washing and the importance of insuring the adequacy of the child's diet with regard to micronutrients that affect lead absorption. The fourth component, used only when a child's blood lead level exceeds 45 μg/dL, is chelation therapy.

Slides 51-56
The recommended actions in response to identification of a child with lead poisoning vary depending on the child's blood lead level.

Slide 57
Chelation is of demonstrated value in reducing a child's blood lead level, but it is not without risks and so it is recommended that it be undertaken only with the assistance of a clinician experienced in applying the protocols. As noted, chelation, unfortunately, does not appear to prevent or reverse the cognitive deficits associated with lead poisoning.

II. Notes on Case Studies

Slide 58
This case study illustrates a classical example of a toddler with prolonged environmental exposure to lead, in this case from an occupational source related to an automobile repair shop. His mother was exposed there from the recycling of car batteries. She carried lead with her from the workplace on her dress and hands. This caused chronic lead exposure in her son.

The impairment in growth and neurodevelopmental behavior is a hint of the long duration of lead poisoning (several months).

Ref:
•ATSDR. *Case Studies in Environmental Medicine. Lead Toxicity,* 2000 *(available at: www.atsdr.cdc.gov/HEC/CSEM/lead/docs/lead.pdf).*

Slide 59
MCV, mean corpuscular volume in femtolitres.
The child's laboratory evaluation showed moderately elevated BLL, microcytic anemia and no evidence of paint chip ingestion.

Slide 60
Treatment was environmental – eliminating exposure – and correction of nutritional deficit. Within 4 months the abdominal colic was resolved, but the child's small stature and hyperactivity probably represent developmental toxicity from chronic exposure which could be permanent. Prevention is key!

Slide 62
MCV, mean corpuscular volume in femtolitres.
The child's laboratory evaluation showed elevated BLL, and microcytic anemia.

Slide 63
Treatment was environmental – eliminating exposure – and correction of nutritional deficits.

III. Reference slide

Slide 73
CDC Advisory Committee on Childhood Lead Poisoning (ACCLP) recommendations for case management of lead-poisoned children are provided in the "blue" book. These cover medical, developmental, nutritional, and environmental aspects.

Screening guidelines for pediatricians are described in the AAP policy statement, while the screening and management of pregnant or lactating women with elevated lead exposure are described in the 2010 CDC ACCLP statement.

The World Health Organization policies on childhood lead poisoning are described in their 2010 report.

KEY RESOURCES FOR FURTHER READING

American Academy of Pediatrics. Air Pollutants, Outdoor. Pediatric Environmental Health. 2012 pg. 313-327.

American Academy of Pediatrics, Committee on Environmental Health. Ambient air pollution: health hazards to children. Pediatrics. 2004; 114: 1699-1707.

US Environmental Protection Agency. *Air Quality Index: A Guide to Air Quality and Your Health*. Washington, DC: Environmental Protection Agency; August 2009. Publication No. EPA-456/F-09-002. Available at: http://www.epa.gov/airnow/aqi_brochure_08-09.pdf. August 19, 2013.

World Health Organization. Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide: Summary of risk assessment. Global update 2005. Publication No. WHO/SDE/PHE/OEH/06.02. Available at: http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf. August 19, 2013.

***Note:** This User Guide is intended to accompany the PowerPoint module of the same name. It elaborates on some studies which may require more in-depth information than what is provided on the slides. However, the contents of all slides in the module are equally important to present.*

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