

## Recent Advances in the Clinical Management of Lead Poisoning

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**Abstract-** Lead poisoning is a historic universal disease. Acute or chronic lead exposure may cause reversible or even permanent damages in human beings. Environmental lead exposure is a global health concern in children. Occupational lead poisoning is still a health issue, particularly in developing countries. During the last decades, new methods and medications have been advocated for the prevention and treatment of lead poisoning. This review deals mainly with recent developments in the management of lead poisoning. Sources of lead exposure are introduced, and methods for the primary prevention of lead poisoning are discussed. Details for the screening of adults and children are also explained to serve as a practical guideline for the secondary prevention. Standard chelation therapy in different groups and up-to-date less toxic new medications for the treatment of lead poisoning are finally discussed. Our published clinical research on the therapeutic effects of garlic tablets in mild to moderate occupational lead poisoning will also be discussed.

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### Introduction

Lead poisoning (also known as plumbism) is a hazardous environmental and occupational disease that affects millions of children and adults around the world. As occupational lead exposure has been controlled in developed countries, attention has been redirected from high-dose occupational exposure in adults to sub-clinical exposure in children at larger groups (1). Various sources of lead exposure in the environment breastfed babies and workplace (2-4) make lead poisoning a ubiquitous health issue. Ongoing research studies focus on the possible link between blood lead concentration (BLC) and different diseases in children and or in adults, appropriate prevention and clinical management (5).

This review article aimed mainly at advancement in the clinical management of lead poisoning with special reference to our recent clinical findings on the therapeutic effects of garlic tablets in mild to moderate occupational lead poisoning.

### Epidemiology

According to the Centers for Disease Control and Prevention (CDC) lead poisoning is defined as BLC  $\geq$  10  $\mu\text{g}/\text{dL}$ . Between 1978 and 1988, developed countries including Belgium, Germany, New Zealand, Sweden, and the United Kingdom experienced a 25-45 percent

decrease in the average BLC of their adult population (6). Another study shows that the number of children aged 1-5 years with BLC  $\geq$  10  $\mu\text{g}/\text{dL}$  has decreased from 77.8% in 1976 to 1.6% in 2002 in the United States of America (7). Nevertheless, Landrigan *et al.*, (2002) estimated that the cost of lead poisoning in the United States is \$43.4 billion for the one-year cohort of children aged 5 years in 1997 based on cognitive and behavioral complications of lead poisoning (8,9). Although CDC was committed to the goal of eliminating elevated BLC in children by 2010, still approximately 250,000 U.S. children aged 1-5 years have lead poisoning (10). Considering that lead poisoning is becoming a greater concern in underdeveloped and developing countries, the annual cost of lead poisoning in these countries can be much higher. For example, since the late 1970s, the rapid industrialization of China has resulted in the abrupt release of toxic agents to the environment that make lead poisoning a serious health problem (11). Lead poisoning is also prevalent in Latin America and Caribbean countries where leaded gasoline and occupational exposure to lead are increasing due to the rapid urbanization and industrial development (12). In addition, the facts that lead poisoning is a more common disease among refugees, international adoptee and immigrant children in the United States (13,14) indicates its universal importance.

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## Management of lead poisoning

There is, unfortunately, no report on the national statistic of lead exposure in Iran. However, sporadic research has been carried out on the occupational lead poisoning and children exposure to lead. Not being managed in a modern way, mine workers in Iran were commonly exposed to lead over the last five decades. While leaded gasoline in Iran continued to be an important source of lead exposure in the last decades; air quality improvements as well as 70% decrease in children's BLC occurred after the US had banned the use of leaded gasoline in the 1970's (15,16). It is hoping that by using unleaded petrol in Iran, lead exposure due to the air pollution will significantly be declined.

Contaminated foods and adulteration of opium with lead are also considered as threats to human health. Water sources might be polluted to lead and or other heavy metals, affecting drinking and irrigation water quality. The deliberate addition of lead into opium to weight gain has recently resulted in lead toxicity. The patients present with abdominal pain which initially are difficult for the physicians and even gastroenterologists to diagnose the etiology of the pain as lead poisoning. Following consultations with a clinical toxicologist (corresponding author) they are now aware and refer the opium users with abdominal pain to clinical toxicologists for the clinical management of lead poisoning. Jalili and Azizkhani reported 35.2 mg lead in 100 grams of opium being used by an addict showing gastrointestinal disorders. The mentioned amount of lead in opium is not too much, but taking the adulterated opium regularly by the drug abusers leads to clinical toxicity (17).

### Sources of exposure and individuals at risk

Lead is an element that is found in earth's crust. However, when mined and used by men, it is capable of causing hazardous health effects (18). Environmental sources, such as lead-based paint and leaded gasoline, affect the entire population, particularly children, because of their frequent oral mouthing behaviors (19). Deteriorating lead paint and contaminated dust and soil are the primary sources of lead poisoning among U.S. children (13). In addition, leaded gasoline pollutes the air and soil and serves as another environmental source of lead poisoning especially in urban areas with higher traffics (20). It is estimated that leaded gasoline deposited 4-5 million tons of lead in soil in the U.S. (19). However, in developing countries, different sources and pathways of exposure exist. In many Latin American countries as well as in Mexico, lead-glazed ceramics is the sources of exposure. Leaded petrol in

China and India, conventional and cottage lead smelters in Jamaica, and battery plant in Albania and Iran are another source that account for the elevation of BLC in these populations (6,21). Therefore, limiting the environmental (Table 1) and additional sources of exposure (Table 2) requires public health surveillance by governmental and non-governmental agencies as well as educating individuals and families at risk, which differ from one country to another.

In addition, occupational exposure is the most common cause of lead poisoning among adults (25,26). In this setting, inhalation of lead dust and fumes is the most important route of absorption. Besides, ingestion of lead through eating, drinking, and smoking in the workplace may result in elevation of BLC (27). Therefore, strict adherence to industry safety regulation is necessary to limit the occupational exposure. Control of temperature, reduction of aerosol, dust, or fume production, mechanization of the workplace and sufficient local and general ventilation would be helpful in decreasing lead contamination. In addition, worksite safety and personal hygiene, i.e. proper use of protective clothes and equipment, is critical to the prevention of occupational lead poisoning. Workers and family members should also be educated to prevent take-home lead poisoning that is defined the introduction of lead into workers' houses on lead-contaminated clothing (27, 28). Common occupational sources of lead exposure are described in Table 3.

### Primary prevention

Primary prevention is defined as limiting the spread of illness to previously unaffected patients or populations. Preventing lead poisoning before its occurrence is crucial because lead-induced neuro-cognitive deficits are irreversible, and there are concerns about lead remobilization and adverse drug reactions. Even low concentrations of lead can cause permanent damage to developing the brain in children because of their immature blood-brain barrier (19). In children, lead is easily stored and has negative effects on other organs and systems of their body such as the kidneys, bones, blood and nervous systems (14). Since only 1-2% of the total amount of stored lead in the body is removed after a typical course of chelating therapy (31), source identification, and primary prevention play a pivotal role in the fight against lead poisoning.

It is believed that the successful abatement in the prevalence of lead poisoning in the United States is due to a source-oriented approach rather than treatment of symptomatic cases (32). Strategies such as eliminating

lead in gasoline and paint have already been successful in lowering BLC in American children (33). However, the use of leaded gasoline is still common in developing countries (20). In addition to leaded gasoline, other sources of lead poisoning should be recognized, and appropriate measures should be taken to avoid exposure.

For instance, wastes of lead depending plants in the tile, battery, and fluorescent lamp factories can affect air and water quality. Therefore, examination of drinking and agricultural water safety nearby those factories is a deep concern and is being screened for lead and other heavy metals (34,35).

**Table 1. Environmental sources of lead poisoning (13, 22, 23)**

Source	Items
<b>Paint Chips /Dust</b>	Dust containing lead from renovations or remodeling House dust from deteriorated lead paint
<b>Soil</b>	From yards contaminated by deteriorated lead paint lead Industry emissions Roadways with high leaded gasoline usage
<b>Air</b>	Leaded gasoline (previously the dominant source) Industrial emissions (currently the most airborne lead)
<b>Water</b>	Lead-soldered pipes and valves (first-morning draw or hot water); kettles and pots; cooking utensils Water coolers
<b>Food</b>	Stored in Lead-soldered cans Stored in plastic bread bags that contain lead in the printing ink Dietary supplements: <i>Sindoor</i> (orange colored powder, used as dye) <i>Kozhambu</i> (spices from India) <i>Swanuri&amp;Kharchos</i> (spices from Republic of Georgia) <i>Lozeena</i> (spices from Iraq) <i>Paprika</i> (red, powdery condiment derived from dried, ripe sweet peppers) "Moonshine" whiskey and lead foil-covered wines Contaminated foodstuffs: homegrown vegetables, calcium supplements, flour, candy Lead leached from leaded crystal, ceramics, vinyl lunch boxes Breast Milk (due to current and past maternal exposures)

## Secondary prevention

### Pediatric screening

Secondary prevention focuses on identifying asymptomatic people, particularly children with high BLC (2). Children benefit more when interventions for prevention are applied at an early age (36). According to recent studies, no threshold for the harmful effects of lead could be defined because children's physical and mental development can be affected even at BLCs less than 10 µg/dL (14). At this concentration, detection and repair of lead hazards are not mandatory (36). Only good parenting skills and an enriched social environment may ameliorate lead-related negative developmental outcomes (37, 38). Lead-related education about home cleanliness for low-income parents via videotape in a pediatric office is reported to

be effective in increasing knowledge and compliance with preventive measures among these families. However, for children at high risk, more education and nonprofessional cleaning is not effective in preventing the development of BLC  $\geq 10$  µg/dL. In this group, more measures should be taken to find and reduce the source of exposure (39). In the United States, risk evaluation is based on answers to a personal risk assessment questionnaire. According to this questionnaire, at least one positive or skeptical answer to one of the following questions designates the children as high-risk and necessitates screening tests:

- Residence in or regular visit of buildings built before 1950
- Residence in a building built before 1960 with ongoing renovation or remodeling
- Having a sibling or playmate with the past or

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- current lead poisoning.
- High-risk zip codes identified by CDC.
- Living with an adult with occupational or recreational lead exposure, and being refugees, recent immigrant or international adoptee (2,19,22).

Generally, CDC recommends that two routine screenings should be performed. All children enrolled in

Medicaid should receive BLC-screening tests at 12 and 24 months of age. Children aged 36 - 72 months of age who have not been screened previously and high-risk children exposed to sources of lead poisoning as well as those who are classified high-risk by their state or local health departments are required to participate in the BLC-screening tests (36).

**Table 2. Additional sources of lead poisoning**

Source	Items	References
<b>Domestic</b>	Pottery and ceramics, e.g. ceramic dinnerware; lead soldered <i>Samovar</i> urn from Iran (used for boiling water); dust from imported miniblinds; curtain weights; lead-glazed pitcher; jewelries; printers; artificial turf; antique cribs, or furniture; toys e.g. bullets from toy guns or those coated with lead paint; crayons or chalks; decorative exterior home features (e.g., "pewter-look" fencing)	(13,14,23)
<b>Folk remedies</b>	<p><i>Alcohol</i>  <i>Azarcon</i> (bright orange powder thought to be medicinal)  <i>Ba-Baw-San</i> (Chinese herbal medicine used for colic)  <i>Bali bali</i>  <i>Bint Al Zahab</i> (powder mixed with honey and butter for colic)  <i>BintDahab</i> (Saudi Arabian yellow powder used as a home remedy)  <i>Bokhoor</i> (fumes from wood and lead used to calm infants)  <i>Coral</i>  <i>Ghasard</i> (brown powder to aid in digestion)  <i>Greta</i> (Mexican yellow powder to treat gastrointestinal distress)  <i>Jin Bu Huan</i> (Chinese herbal medicinal pain reliever)  <i>Liga</i>  <i>Litarigio</i> (yellow colored lead monoxide powder used as antiperspirant in the Hispanic community)  <i>Pay-loo-ah</i> (Vietnamese red powder to treat fever or rash)  <i>Po Ying Tan</i> (Chinese herbal medicine)  <i>Santrinj</i> (Saudi Arabian red powder used for teething)  <i>Surma</i> (Indian black powder used for teething)  <i>Reuda</i>  Ayurvedic medicine (traditional medicine from Tibet)  Saudi traditional medicine (orange powder for teething)  Tibetan herbal vitamin (used for brain health)</p>	(2,14,19)
<b>Cosmetics</b>	<p><i>Ceruse</i>  <i>Kohl</i> (a type of eyeliner from India, the Middle East, and Africa)  <i>Surma</i> (powder applied to the eyes, from India)  Eye cosmetics from Pakistan</p>	(2,14,23)
<b>Drug of abuse</b>	Methamphetamine, heroin; leaded gasoline huffing	(24)

When BLC is 10 - 19  $\mu\text{g/dL}$ , dietary and environmental interventions and a second follow-up BLC within one month are recommended. If BLC increases or remains between 15-19  $\mu\text{g/dL}$  for 3 months or the first BLC is between 20- 44  $\mu\text{g/dL}$ , clinical and laboratory workup is indicated. In this case, a complete history, physical examination and measurement of iron and hemoglobin are required. Iron-deficient children should take a daily dosage of 4-6 mg/kg iron. Neuro-developmental monitoring is also recommended (14).

### Occupational screening

Workers who handle materials with a significant lead content are expected to have lead exposure through inhalation or by ingestion. It is thus recommended that a baseline medical history and physical examination as

well as a measurement of BLC and serum creatinine be performed before commencement of the occupation and at a regular interval based on the level of lead exposure. Further surveillance recommendations for lead-exposed workers based on specific BLCs are summarized in table 4 (31).

### Dietary management

Some dietary deficiencies increase the risk of lead poisoning in children. For example, iron deficiency is associated with elevated BLC. Therefore, CDC recommends assessment of iron status and placing iron-rich diet on all children with lead poisoning (2). In addition, some studies suggest that iron is able to decrease BLC in children with or without iron deficiency (2). However, some studies show no

correlation between BLC and iron deficiency (40,41). This may be due to low sample size being investigated than the predecessor studies.

Similarly, calcium (1200 mg/day of elemental calcium as calcium carbonate) inhibits the lead absorption and decreases its bioavailability (14,19). It

also decreases the lead content in mother's breast milk (13). Zinc deficiency worsens the toxicity caused by lead poisoning. Zinc, vitamin C, protein and phosphorus deficiency increase the absorption of ingested lead (2,14).

**Table 3. Occupational sources of lead exposure that is also considered the causes of take-home exposure**

Source	Reference	Source	Reference	Source	Reference
Automobile radiator repairers	(2,6)	Automobile factory workers and mechanics	(19)	Ceramic crafts	(2,6,22,29)
Crystal glass makers	(6, 13)	Enamellers	(6)	Furniture refinishing, restoring	(2,14,22)
Firing range instructors	(30)	Glass blowers	(6)	Home remodeling, refinishing	(2,13,14,22)
Bullet salvagers	(29)	Lead miners	(19)	Painting (fine artist's pigments)	(13,14,29)
Lead smelters, refiners	(6,29)	Plumbers	(13,22)	Target shooting, recasting lead for bullets	(14)
Wire and cable workers: Wire patenting Cable making	(6,13)	Pottery glazers	(13,14,29)	Stained glass making	(13,14,29)
Painters, construction workers (sanding, scraping, or spraying of lead paint; demolition of lead-painted sites)	(1,14)	Traffic police officers, taxi drivers, garage workers, turnpike tollbooth operators, gas station attendants that are exposed to leaded gasoline exhaust fumes* Rubber product manufacturers	(6,13,19,29)	Metal welders, cutters (includes bridge and highway reconstruction workers)	(14,29)
Polyvinyl chloride plastic manufacturers	(6,13)	Solderers	(6,13)	Pipe fitters	(14)
Ship-breakers Ship repairers	(6,14)	Type founders	(6,19,29)	Electronics manufacturers	(13,23)
Storage battery manufacturers, repairers, recyclers	(6,13,29)		(6)	Jewelers	(2,6,13)

\* Unlikely now in the United States, but is still a hazard in developing countries

### Treatment

The first and most critical step in the treatment of lead poisoning is the removal of patients from the site of exposure and elimination of possible sources of lead. In adults, removal is indicated when BLC does not decrease below 10 µg/dL over an extended period, remains ≥ 20 µg/dL for 4 weeks, or at anytime ≥ 30 µg/dL (31). Dietary deficiencies should also be corrected as noted above especially in childhood plumbism.

The indication and type of pharmacologic treatment are determined by patient's age, clinical symptomatology and BLC (1,19). Patients with BLC < 40 µg/dL and significant symptoms and signs of lead poisoning should receive oral chelating therapy. Adults with BLC

between 40 and 79 µg/dL should be referred for prompt medical evaluation. When BLC raises more than 80 µg/dL immediate or urgent medical evaluation for probable chelating therapy is indicated. For BLC ≥ 100µg/dL, chelating therapy is always necessary and should be started as parenteral in a hospital (31).

On the other hand, in children, chelating therapy is indicated when lead concentrations in two venous blood samples are more than 45 µg/dL even the child is asymptomatic. There should be a 24-48-hour interval between the two sampling. Children should be hospitalized for parenteral treatment if BLC ≥ 70 µg/dL (19).

**Table 4. Health-based surveillance recommendations for workers exposed to blood lead concentration (31)**

BLC (µg/dL)	Recommendation
< 10	<ul style="list-style-type: none"> <li>• Measure BLC every month for 3 months or in case of higher lead exposure due to change in the task. Then every 6 months, if the BLC increase is less than 5 µg/dL in 3 months.</li> <li>• Evaluate the exposure and protective measures, if BLC increase is <math>\geq 5</math> µg/dL. Also consider increasing monitoring.</li> <li>• Evaluate the exposure and protective measures, if BLC is 5 - 9 µg/dL for women who are pregnant or intend to become pregnant.</li> <li>• As for BLC &lt; 10 but measure BLC every 3 months.</li> <li>• Evaluate and reduce exposure. Consider removal if no improvement with exposure reduction or in case of medical conditions such as chronic renal disease, hypertension, neurological disorders and cognitive dysfunction.</li> </ul>
10 - 19	<ul style="list-style-type: none"> <li>• Back to 6 months measurement intervals, if 3 consecutive BLCs &lt;10 µg/dL.</li> <li>• Measure BLC monthly</li> </ul>
$\geq 19$	<ul style="list-style-type: none"> <li>• Remove the worker from exposure if a repeated BLC is still <math>\geq 19</math> µg/dL after 4 weeks or if a BLC is <math>\geq 30</math> µg/dL.</li> <li>• Consider a return to work if 2 consecutive BLCs are &lt;15 µg/dL.</li> </ul>

**Chelating agents**

To date, the use of dimercaprol or British Anti-Lewisite (BAL), calcium disodium ethylenediaminetetraacetic acid (CaNa<sub>2</sub>EDTA), D-penicillamine and Meso-2,3-dimercaptosuccinic acid (DMSA) named succimer is approved for the treatment, but not prevention (42), of acute and chronic lead poisoning (19). The chelating agent dosages and indications in pregnancy and lactation are summarized in Table 5.

BAL is one of the oldest agents that were used in the treatment of lead poisoning (45). It is administered intramuscularly (IM) 2.5 mg/kg per day in two divided doses. The duration of treatment is at least three days. BAL facilitates the excretion of zinc from urine (19). Other adverse effects are prolonged partial thromboplastin time, leukopenia, hemolysis, renal and liver toxicity, gastrointestinal disturbance, hypertension, headache, hyperpyrexia and painful injection (deep intramuscular). BAL is contraindicated for patients with Glucose-6-phosphate dehydrogenase deficiency. Painful abscesses at the injection site are reported. Skin contact with BAL produces immediate pain and blistering. Eye contact can even result in blindness (46). These severe and frequent adverse effects (50% after receiving 5mg/kg) impose considerable limits on the routine use of BAL (19,45). It is only indicated for BLC  $\geq 70$  µg/dL or in combination with CaNa<sub>2</sub> EDTA in the treatment of lead encephalopathy (19).

CaNa<sub>2</sub> EDTA does not cross the blood-brain barrier to any major extent but mobilizes lead in kidneys, liver,

and particularly in bones. Therefore, CaNa<sub>2</sub> EDTA is able to remove lead from the extracellular compartment. Calcium ions displace lead cation (47). CaNa<sub>2</sub> EDTA combined with a maximal dose of BAL is parenterally administered in the treatment of lead encephalopathy along with supportive care (48,49). It is also the preferred chelating agent in pregnancy but is a second-line therapy for BLC  $\leq 70$  µg/dL (19,44). The duration of treatment is five days. A single daily dose of CaNa<sub>2</sub> EDTA (50mg/kg or 1000 mg/m<sup>2</sup>) should be infused continuously over 6-12 hours. Since each milliliter of the ampoule contains 200 mg CaNa<sub>2</sub> EDTA, every 5 mL ampoule can be diluted in 250 to 500 mL normal saline or Dextrose 5% in water. The maximum treatment dosage is 1g per day (19). The adverse effects of CaNa<sub>2</sub> EDTA are dose-related. Nephrotoxicity, hypokalemia, and depletion of zinc and copper are among the toxic effects. CaNa<sub>2</sub> EDTA nephrotoxicity can be reduced by adequate hydration (19,47).

D-penicillamine is a reductive chelator. By reducing lead or copper cations, it decreases their binding affinity to proteins and finally stimulates their excretion in urine. D-penicillamine is the drug of choice for the treatment of Wilson’s disease (50). However, because of several reports of life-threatening adverse reactions, such as renal or bone marrow dysfunction (which leads to leukopenia and thrombocytopenia), and dermatologic complications, D-penicillamine is considered a third-line drug for the treatment of lead poisoning (14,19,22). It is used when chelation is necessary and unfavorable adverse reactions result from DMSA and CaNa<sub>2</sub> EDTA.

It is also used in reduced dosage (15 mg/kg per day orally) for the treatment of pediatric mild-to-moderate lead poisoning (43). In adult lead poisoning, a 250 mg

capsule of D-penicillamine is administered 4 times daily. The duration of treatment for adults and children is 4 to 12 weeks (19).

**Table 5. Standard chelating agents for the treatment of lead poisoning and indications in pregnancy and lactation (14, 19, 31, 43)**

Chelating agent	Indication	Dosage	Pregnancy	Lactation
<b>Dimercaprol</b>	BLC $\geq$ 70 $\mu\text{g}/\text{dL}$ (Adjunct with $\text{CaNa}_2$ EDTA if BLC > 100 $\mu\text{g}/\text{dL}$ )	4-5 mg/kg every 4 hour for 3-5 days	Category C*	Safety not established
<b><math>\text{CaNa}_2</math> EDTA</b>	BLC $\geq$ 45 $\mu\text{g}/\text{dL}$ Or lead encephalopathy	1000 mg/m <sup>2</sup> /day or 50 mg/kg for 5 days (maximum 1 g/day) IV (in normal saline or D5W) over 8-12 hours IM every 8-12 hours Could be repeated after 2-4 day rest period.	Category C (But is the preferred agent)	Safety not established
<b>D-penicillamine</b>	BLC 45 to 69 $\mu\text{g}/\text{dL}$	Adults: 250 mg every 6 hours Children > 6 months: 10-15 mg/kg for 4-12 weeks	Contraindicated	Contraindicated
<b>DMSA</b>	BLC 45 to 69 $\mu\text{g}/\text{dL}$	10 mg/kg or 350 mg/m <sup>2</sup> every 8 hours for 5 days; then reduce to every 12 hours for 14 days. Could be repeated after a 2-week rest period. 30 mg/kg/day for at least 5 days with at least 1 week rest period (more efficacious (44)) Not recommended for children < 12 months	Category C	Contraindicated**

BLC: blood lead concentration;  $\text{CaNa}_2$  EDTA: calcium disodium ethylenediaminetetraacetic acid; DMSA: 2-3 mesodimercaptosuccinic acid (succimer); IV: intravenous; IM: intramuscular; D5W: dextrose 5% in water

\*Human studies are lacking, animal studies are either positive for fatal risk or lacking. Although risk cannot be ruled out, benefits may justify the potential risks. \*\*Lactation should be discouraged during treatment with succimer

Succimer (DMSA) is also not able to cross blood-brain barrier. The mechanism of chelation by DMSA is not clearly explained but it principally, if not exclusively, chelates lead in the kidney (47). DMSA is the first choice for the treatment of mild and asymptomatic pediatric lead poisoning. Each course of treatment takes 19 days. For adults and children older than 12 months, 100 mg capsules of DMSA are administered at 10 mg/kg (350 mg/m<sup>2</sup>) every 8 hours for 5 days. For the next 14 days, the same dosage is administered every 12 hours. A second 19-day treatment course can be repeated after a 2-week was out period. Children should be protected from lead exposure during treatment with Succimer (19). It can be considered an alternative for the treatment of lead encephalopathy when the oral route is preferred (47). Although DMSA is not teratogenic, it can produce maternal toxicity by decreasing weight gain (44). Other adverse effects of DMSA are a transient increase in hepatic transaminases activity, neutropenia, abdominal cramping and severe

mucocutaneous reaction. The latter necessitates discontinuation of therapy. The effect of DMSA on depletion of zinc and copper is fewer than  $\text{CaNa}_2$  EDTA (19,47).

#### **New and less toxic medications:**

Although other drugs than the above chelating agents have been recommended in the treatment of lead poisoning, more evidence is needed in favor of their safety and efficacy to advocate their use as an alternative or adjunct therapy for the standard pharmacological treatment. The recommended medications are as follows:

Thiamine (25-50 mg/kg/day) is a water-soluble vitamin that, in combination with  $\text{CaNa}_2$  EDTA (50 mg/kg/day) for 3 days, enhances the elimination of lead from liver and kidney (51,52) and decreases the oxidative damage caused by lead toxicity (53). Similarly, Vitamins C and E reduce lead-induced oxidative stress (53,54).

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N-acetylcysteine (NAC) is also considered an antioxidant chelator. It possesses reactive groups, such as thiol, hydroxyl, and amine, which can bind with lead and remove it from the body (55-57). NAC is administered 800 mg/kg/day for 5 weeks (57). A recent in vitro study has demonstrated that N-acetylcysteine amide (NACA) has a higher cellular permeability, better systemic bioavailability, and higher binding affinity to lead compared to NAC, and, therefore, is considered a preferable alternative (55).

Taurine is an organic acid and a major constituent of bile. Single therapy with taurine does not reduce lead burden; however, the concomitant administration of taurine (50-100 mg/kg once daily for 5 days) with a standard thiolchelator (DMSA 50 mg/kg once daily for 5 days) has been effective for the treatment of sub-chronic lead poisoning (58).

Alpha-lipoic acid (50 mg/kg/day), methionine (100 mg/kg/day), homocysteine (25 mg/kg/day) are other sulfur-containing compounds which are able to reduce oxidative stress in lead-exposed tissues when administered for 5 weeks (57).

Garlic (*Allium sativum*) is an herbal product which is considered to have chelating effect in some animal studies (54, 59, 60). In a controlled double-blind clinical trial on 117 battery plant workers performed by the authors, garlic was significantly effective in reducing BLCs ( $P = 0.002$ ) in patients with chronic mild-to-moderate lead poisoning. Furthermore, a number of neurological signs and symptoms such as irritability ( $P = 0.031$ ), headache ( $P = 0.028$ ) and decreased DTR ( $P = 0.019$ ) were decreased (61). Dried powder garlic (400 mg; equivalent to 1200  $\mu\text{g}$  allicin or 2 g fresh garlic) was administered 3 times daily for 4 weeks. The frequency of adverse effects was significantly ( $P = 0.023$ ) lower in the garlic group compared to those who took D-penicillamine 250 mg, three times daily (61).

After the course of chelation therapy, a thorough neurological examination should be performed in order to assess the clinical response to treatment. Measurement of free erythrocyte and zinc protoporphyrin (ZPP) is also suggested for the assessment of response to clinical management (19).

A study on children by which their parents were workers of lead-related factories revealed high BLC ( $163.81 \pm 57.19 \mu\text{g/L}$ ). It was then focused on renal clearance of lead by coriander (*Coriandrum Sativum*) in a case-control group. Even though, the group taking coriander had a decrease in BLC, the second group - taking placebo - also showed a significant decrease in BLC. As a result, it seemed that coriander is not effective in lead

elimination, although the previously animal experiment on mice reported as an effective medication. The study was apparently a double-blind investigation, but the children mothers realized that drop medication is coriander and gave coriander fresh herb to the placebo group. It was thus recommended to study more in both adults and children with more controls to find out the effect of coriander in human lead poisoning (62).

Since lead is a toxic element that is stored in the body, and its removal is almost impossible, preventive measures are very important. Chelation therapy is still the standard treatment for lead poisoning. However, new less toxic medications such as garlic tablet can be used for the treatment of mild-to-moderate lead poisoning.

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