

Management of Childhood Lead Poisoning: A Survey

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ABSTRACT. Published recommendations (1985) for the management of childhood lead poisoning suggest the use of ethylenediaminetetraacetic acid (EDTA) provocation testing and chelation as the mainstay of treatment for blood lead levels between 25 and 55 $\mu\text{g}/\text{dL}$. Since 1985 evidence has accumulated indicating that (1) levels of blood lead less than 25 $\mu\text{g}/\text{dL}$ are detrimental to cognitive development, (2) EDTA provocation testing may result in potentially harmful shifts in the body lead burden, and (3) oral agents such as penicillamine and 2,3-dimercaptosuccinic acid are effective in reducing elevated lead levels. To determine how this evidence impacts on the management of childhood lead poisoning, the authors surveyed the lead poisoning clinics of pediatric departments in the cities estimated by the United States Public Health Service to have the largest number of children affected by lead poisoning. Thirty (70%) of 43 surveys were completed. Respondents indicated that the lowest blood lead level for which they would use a chelating agent to reduce the lead burden was as follows: 50 $\mu\text{g}/\text{dL}$ (3%), 45 $\mu\text{g}/\text{dL}$ (3%), 40 $\mu\text{g}/\text{dL}$ (13%), 35 $\mu\text{g}/\text{dL}$ (3%), 30 $\mu\text{g}/\text{dL}$ (27%), 25 $\mu\text{g}/\text{dL}$ (47%), and 20 $\mu\text{g}/\text{dL}$ (3%). For all blood lead levels from 20 through 55 $\mu\text{g}/\text{dL}$, EDTA was the most frequently recommended chelating agent (chelation and provocation testing). Fifteen percent of responding lead clinics do not use the provocation test under any circumstances. For a child with a negative EDTA provocation test, the percentage of respondents recommending the use of any chelation therapy ranged from 16% for blood lead levels of 25 through 29 $\mu\text{g}/\text{dL}$ to 66% for levels of 50 through 55 $\mu\text{g}/\text{dL}$. Orally active chelating agents are used by fewer than one third of the responding lead clinics and were selected as the chelating agent of choice at all blood lead levels from 25 through 55 $\mu\text{g}/\text{dL}$ by at least one respondent. The results of this survey indicate the following: (1) There is a wide range of blood lead levels for which chelation therapy is recommended. (2) The majority of children with elevated lead burdens are managed using EDTA. (3) The EDTA provocation test continues to be widely used. (4) The majority of children with blood lead levels of 25 through 44 $\mu\text{g}/\text{dL}$ with negative provocation tests do not receive chelation therapy. (5) Orally active chelating agents are used in the minority of lead clinics. (6) No common approach for the treatment of lead toxicity appears to exist. (7) In the majority of pediatric centers, current management of blood lead elevation does not appear to reflect new information regarding the effects and treatment of lead poisoning. *Pediatrics* 1992;89:614-618; lead poisoning, treatment, chelation.

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Presented, in part, at the 31st annual meeting of the Ambulatory Pediatric Association, New Orleans, LA, May 1, 1991.

Received for publication Mar 15, 1991; accepted Jun 12, 1991.

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ABBREVIATIONS. CDC, Centers for Disease Control; EDTA, ethylenediaminetetraacetic acid; DMSA, 2,3-dimercaptosuccinic acid.

In 1985 the Centers for Disease Control (CDC) released guidelines for the management of childhood lead poisoning.¹ This statement, entitled "Preventing Lead Poisoning in Young Children,"¹ was issued with an appendix consisting of a consensus report on management criteria for elevated lead burdens in children.² The consensus report recommends the use of CaNa₂-ethylenediaminetetraacetic acid (EDTA) provocation testing and chelation as the mainstay of treatment for children with blood lead levels between 25 and 55 $\mu\text{g}/\text{dL}$.² In the 1987 "Statement on Childhood Lead Poisoning" issued by the American Academy of Pediatrics,³ the recommendations for medical intervention were also derived from the CDC statement. Although revised guidelines were issued in 1991, the 1985 statement indicates the most current official recommendations of the CDC that were available at the time this study was completed.

Since the 1985 CDC and 1987 American Academy of Pediatrics statements were released, additional data have accumulated which may impact on therapeutic decisions for children with elevated lead burdens. First, although it has been well recognized for many decades that children with symptomatic lead poisoning and those with very high levels are at risk for neuropsychologic deficits, only recently have the data regarding lower exposure levels been sufficiently well controlled to indicate clearly that low-level lead poisoning during childhood is associated with cognitive deficits.⁴⁻¹¹ Some studies indicate that even blood lead levels well below 25 $\mu\text{g}/\text{dL}$ are associated with impaired cognitive outcomes.^{10,12,13}

Second, the use and safety of the EDTA mobilization test have recently come under increased scrutiny following publication of a study on the effects of EDTA on the redistribution of lead stores.¹⁴ It has been demonstrated that in a rat model of chronic low-level lead exposure, levels of brain lead are increased by 100% over baseline values following a single EDTA dose in a situation that closely mimics EDTA provocation testing protocols.¹⁵ This study raises additional concerns about EDTA chelation because there is no net decrease in brain lead levels following a 5-day EDTA chelation protocol, despite an overall decrease in body lead burden.

Third, although the 1984 consensus statement describes the use of penicillamine for the treatment of childhood lead poisoning, it does not indicate in what situations, if any, penicillamine would be an appropriate or the preferred chelating agent for use in

children with elevated lead burdens. Although there were published reports regarding the use of oral penicillamine in children with lead poisoning as early as 1970,¹⁶⁻¹⁸ there are more recent data that indicate that penicillamine is effective in reducing blood lead levels in children with blood lead levels of 20 to 40 $\mu\text{g}/\text{dL}$.^{19,20}

Finally, in the CDC report, 2,3-dimercaptosuccinic acid (DMSA) is mentioned briefly as a potentially promising, alternative but investigational agent. There are recent studies that suggest that DMSA may be a safe and effective orally active therapy for the treatment of childhood lead poisoning.²¹⁻²³ Although only recently approved by the US Food and Drug Administration, DMSA has been available for the treatment of heavy metal poisonings in children, including lead poisoning, on a compassionate use basis for the past several years.

To determine what current management strategies for the treatment of childhood lead poisoning are used in the United States, we conducted a nationwide survey of pediatric lead poisoning treatment programs. We hypothesized that information that has accumulated since 1985 about the effects of low-level exposure, concerns regarding EDTA use, and the use of orally active chelating agents would significantly alter the management of children with elevated lead burdens.

METHODS

A written questionnaire inquiring about the management of childhood lead poisoning was distributed to 43 directors of lead clinics of medical school-affiliated pediatric departments. Programs were selected to include all programs that are located in the 18 Standard Metropolitan Statistical Areas that are estimated by the Agency for Toxic Substances and Disease Registry of the United States Public Health Service to have the greatest number of children aged 0.5 to 5 years old who are living in pre-1950 housing and thus are at particular risk for elevated lead burdens. These 18 Standard Metropolitan Statistical Areas are estimated to include a total of more than 2 million infants and young children living in pre-1950 housing (Table 1).

Questionnaires were completed anonymously, with respondents indicating that the survey instrument had been completed by returning a separate number-coded card. A follow-up questionnaire was sent to program directors who did not respond to the first mailing.

RESULTS

Thirty (70%) of the 43 departments surveyed responded to the questionnaire. Responses were received from departments representing all geographic areas surveyed.

Clinic Characteristics

Patients who are evaluated and treated for lead poisoning are seen in a general pediatric clinic in 14 (47%) institutions, a designated lead clinic in 13 (43%) departments, a hematology clinic in 2 (7%) institutions, and in the City Health Department in 1 (3%) pediatric department. Children with lead poisoning have needs that often go beyond those managed by medical interventions alone, as indicated by the wide variety of professional staffing in the lead clinics surveyed (Table 2). Patient volume varies among the departments surveyed, with more than half the clinics

TABLE 1. Ranking of 1980 Census Standard Metropolitan Statistical Areas (SMSAs) by Number of Children 0.5-5 Years Old Living in Pre-1950 Housing*

SMSA	Children 0.5-5 Years	
	No. in Pre-1950 Housing	% of Children in SMSAs
New York, NY-NJ	422 800	60.1
Chicago, IL	271 500	43.2
Los Angeles-Long Beach, CA	225 700	33.5
Philadelphia, PA	172 500	46.4
Detroit, MI	141 900	37.8
Boston, MA	110 400	62.7
Newark, NJ	80 300	53.1
Cleveland, OH	75 100	49.1
San Francisco-Oakland, CA	74 800	32.3
Pittsburgh, PA	71 300	47.4
St Louis, MO-IL	69 200	34.0
Minneapolis-St Paul, MN-WI	60 000	32.2
Baltimore, MD	56 700	34.2
Milwaukee, WI	53 100	43.5
Nassau-Suffolk, NY	51 100	26.5
Washington, DC-MD-VA	48 900	20.9
Buffalo, NY	46 800	51.3
Cincinnati, OH-KY-IN	44 300	35.4
Total	2 076 400	

* Source: Agency for Toxic Substances and Disease Registry.³³

TABLE 2. Professional Staffing of Lead Clinics

Professionals Participating in Lead Clinic	No. (%) of Clinics (N = 30)
General pediatrician	26 (87)
Toxicologist	7 (23)
Hematologist	3 (10)
RN/LPN	23 (78)
Social worker	16 (53)
Lead/environmental inspector	11 (37)
Developmental specialist	4 (13)

seeing fewer than 5 patients in an average week and one third of the clinics seeing 11 or more patients per week.

Blood Lead Levels for Medical Intervention

The lowest blood lead level for which the use of a chelating agent was recommended to reduce the lead burden in an otherwise healthy, asymptomatic child ranged from 20 through 50 $\mu\text{g}/\text{dL}$. One half of respondents indicated that their threshold for medical intervention was above the 1985 CDC limit for the definition of lead poisoning (25 $\mu\text{g}/\text{dL}$) (Fig 1).

Chelating Agents for Initial Management

For all blood lead levels from 25 through 55 $\mu\text{g}/\text{dL}$, EDTA was the most frequently recommended chelating agent. The EDTA provocation test is used most often when blood lead levels are between 30 and 44 $\mu\text{g}/\text{dL}$. Penicillamine was selected as the preferred chelating agent at all blood lead levels from 20 through 55 $\mu\text{g}/\text{dL}$ by at least one respondent, although not the same respondent(s) at all levels, but is used under any circumstances by only 27% of lead clinics. At the time of survey completion, DMSA had not yet been approved for use in the treatment of childhood lead poisoning by the Food and Drug Administration and was used by a single clinic only,

through participation in a special project. There were a large number of comments, however, indicating interest in using DMSA once it is approved and additional safety and efficacy data are available. The frequency of recommendations for initial therapy of blood lead levels from 20 through 55 $\mu\text{g}/\text{dL}$ is shown in Table 3.

EDTA Provocation Testing

The EDTA provocation test was frequently recommended to determine the need for EDTA chelation for all blood lead levels between 25 and 55 $\mu\text{g}/\text{dL}$ as indicated in Table 3. For a child with a negative EDTA provocation test, with the following blood lead levels, the percentage of respondents recommending the use of any chelation therapy was as follows: 25 through 29 $\mu\text{g}/\text{dL}$ (16%), 30 through 34 $\mu\text{g}/\text{dL}$ (23%), 35 through 39 $\mu\text{g}/\text{dL}$ (31%), 40 through 44 $\mu\text{g}/\text{dL}$ (42%), 45 through 49 $\mu\text{g}/\text{dL}$ (57%), and 50 through 55 $\mu\text{g}/\text{dL}$ (66%) (Fig 2). Among those recommending chelation therapy for a child with a negative provocation test, penicillamine was the agent most frequently recommended when the blood lead level is less than 40 $\mu\text{g}/\text{dL}$, and EDTA when the blood lead level is 40 $\mu\text{g}/\text{dL}$ or above. Four (15%) lead clinics indicated that they do not use the provocation test under any circumstances.

Penicillamine Use

Penicillamine is used in eight (27%) of the responding lead clinics. Of those clinics that use penicillamine, moderate abnormality on urinalysis (eg, > 5 red blood cells per high-power field) was the contraindication

most frequently cited (88%), followed by significant lead violations in the child's home (75%), concurrent iron therapy (38%), concurrent antibiotic therapy (38%), and acute minor illness (38%).

DISCUSSION

The results of this survey indicate that no common approach for the treatment of any aspect of low-level lead poisoning appears to exist in the lead clinics of academic medical centers in locations where childhood lead poisoning is most prevalent. There is a wide range of lead levels for which intervention is recommended among these centers, ranging from 20 to 50 $\mu\text{g}/\text{dL}$. Although there are individuals who continue to dispute the data that low-level lead poisoning is associated with impaired cognitive development,^{24,25} the overall consensus is that elevated lead burdens in childhood of 25 $\mu\text{g}/\text{dL}$,^{4-9,11} and probably lower,^{10,11,13} can result in adverse neurodevelopmental outcomes. However, it is not known whether chelation of low-level lead poisoning is beneficial in reversing or preventing the neurotoxic effects of lead. Although the potential risks and benefits of chelation therapy are not yet fully quantified, it is important to weigh these factors based on currently available information when considering pharmacologic intervention in lead-poisoned children. A well-designed, controlled study to determine the effectiveness of various chelation strategies in reducing neuropsychologic morbidity is needed.

The use of the EDTA provocation test varies significantly among the responding lead clinics. At some institutions the test is used at all levels of lead expo-

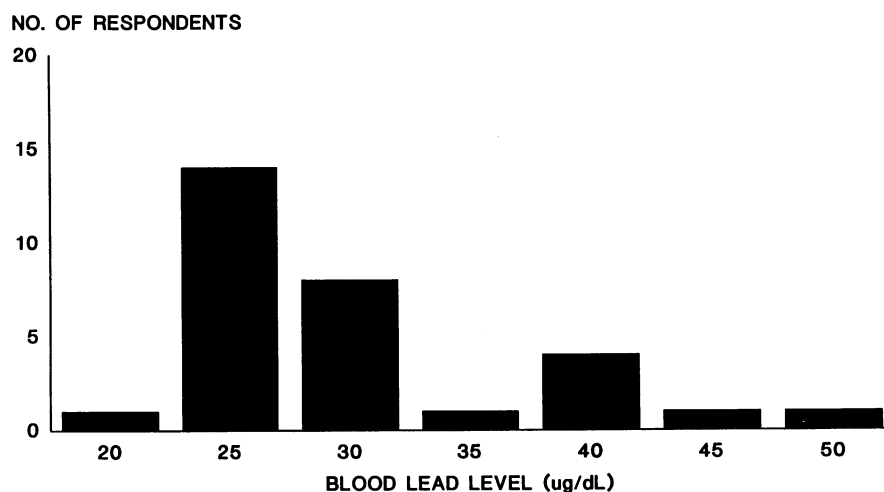


Fig 1. Lowest blood lead levels for which chelation therapy is recommended.

TABLE 3. Initial Management of Lead Poisoning at Various Blood Lead Levels*

Recommended Management	Blood Lead Levels ($\mu\text{g}/\text{dL}$)						
	20-24	25-29	30-34	35-39	40-44	45-49	50-55
No chelation	28 (97)	15 (52)	7 (24)	6 (21)	2 (7)	1 (4)	0 (0)
EDTA provocation test	0 (0)	8 (28)	15 (52)	16 (55)	14 (50)	11 (39)	7 (25)
EDTA chelation	0 (0)	1 (3)	2 (7)	3 (10)	11 (39)	15 (54)	20 (71)
Penicillamine chelation	1 (3)	4 (14)	4 (14)	3 (10)	1 (4)	1 (4)	1 (4)
DMSA chelation†	0 (0)	1 (3)	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)

* Results given as No. (%). EDTA, ethylenediaminetetraacetic acid; DMSA, 2,3-dimercaptosuccinic acid.

† Special project.

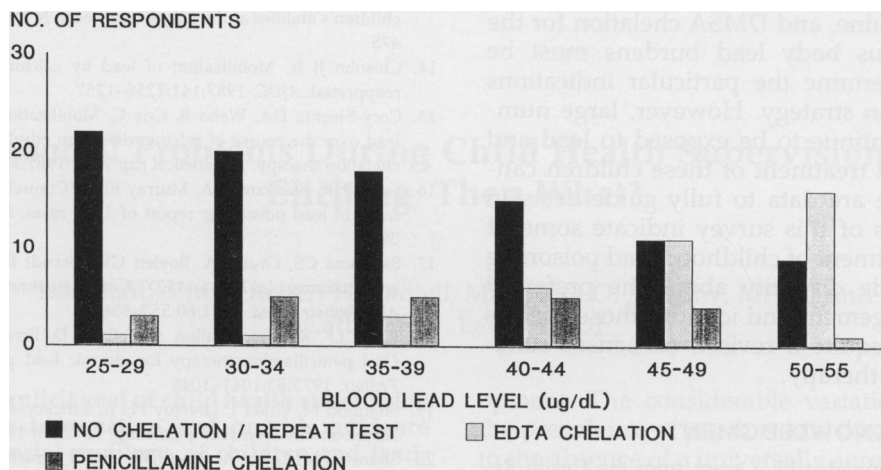


Fig 2. Recommended therapy for a child with a negative provocation test according to blood lead level. EDTA, ethylenediaminetetraacetic acid.

sure from 25 through 55 $\mu\text{g}/\text{dL}$, as recommended by the 1984 consensus statement; in others the test is never used. EDTA provocation testing is the most frequently used initial management strategy for children with lead levels of 30 through 44 $\mu\text{g}/\text{dL}$, but almost half of lead-poisoned children in this exposure range will be managed in some other way. Provocation testing can be cumbersome to carry out, requires a large amount of nursing supervision, particularly in non-toilet-trained children, and can yield an uninterpretable result even under well-controlled conditions.²⁶ It is not known whether the frequency of EDTA mobilization testing reflects the technical difficulties in test administration, concern about potentially harmful shifts in the lead burden as seen in the rat model, or a combination of both factors.

One group of investigators has demonstrated that in children with positive provocation tests, unstimulated urinary lead excretion has a high degree of correlation with excretion following EDTA provocation,²⁷ but it is not known whether this relationship exists in children with a negative mobilization test. If unstimulated urinary lead excretion is determined to be a valid marker for EDTA mobilization testing, this may bypass some of the concerns and difficulties associated with provocation testing. x-Ray fluorescence has recently been promoted as an alternative, noninvasive, and rapid method of determining body lead burden,^{28,29} and wider use of x-ray fluorescence to determine body lead burden may also decrease the frequency of EDTA mobilization testing.²⁹ Despite theoretical advantages of x-ray fluorescence over EDTA mobilization testing, at present it is an experimental method and the clinical applicability of this measurement for the management of lead-poisoned children is unknown. Until additional data accumulate it is likely that EDTA provocation testing will continue to be used under certain circumstances. Refinements of the current recommendations must be based on the accumulated experience and data from EDTA provocation test results and response to EDTA chelation, and the potential hazards of shifts in the lead burden should be considered.

At the time this survey was distributed, orally active lead-chelating agents were used in fewer than one

third of the responding lead clinics, despite the recognition in the 1984 consensus statement that penicillamine may be a useful chelating agent. With the large numbers of children with lead burdens between 25 and 45 $\mu\text{g}/\text{dL}$, increased use of chelating agents other than EDTA will be needed if it is a desired goal to reduce children's blood lead levels below 25 $\mu\text{g}/\text{dL}$, because EDTA provocation testing is rarely positive in children with lead levels in the 25- to 35- $\mu\text{g}/\text{dL}$ range,^{29,30} and EDTA is a less effective chelating agent with decreasing blood lead levels.

Although penicillamine has been shown to reduce effectively the blood lead level in children with low-level poisonings, its use is associated with a high rate of adverse effects and nonresponse.¹⁹ In addition, there are animal data to suggest that there is a significant redistribution of lead during short-term penicillamine administration (intravenous) from bone to soft tissue, indicating perhaps that the desired reduction in brain lead levels may not occur³¹ or might occur only as a secondary effect as postulated with EDTA chelation.^{15,32} Despite these potential concerns, penicillamine is likely to remain an effective drug in the armamentarium for the treatment of lead-poisoned children, but its particular role needs to be clarified.

The initial data on DMSA, while promising, are based on a limited number of children and on children with blood lead levels well above 25 $\mu\text{g}/\text{dL}$.²³ Although DMSA has recently received Food and Drug Administration approval for chelation in lead-poisoned children with blood lead levels above 45 $\mu\text{g}/\text{dL}$, extensive experience with the drug in children is not yet available. The circumstances for which it is the preferred chelating agent are unknown.

The results of this survey are applicable to the care of lead-poisoned children in academic medical centers only, and they do not indicate how children with lead poisoning are managed in the community setting. No information is available about how children with elevated lead burdens are managed outside academic institutions.

There are many unanswered questions regarding childhood lead poisoning and its treatment, and such questions will need to be addressed with further research. Specifically, the relative benefits and risks

of EDTA, penicillamine, and DMSA chelation for the treatment of various body lead burdens must be investigated to determine the particular indications for a given chelation strategy. However, large numbers of children continue to be exposed to lead and its toxic effects, and treatment of these children cannot wait until there are data to fully guide decision making. The results of this survey indicate some of the areas in the treatment of childhood lead poisoning where there is wide disparity about the preferred approach for management and identify those aspects of treatment that require a revised consensus statement to help guide therapy.

ACKNOWLEDGMENT

This research was supported by a grant from the Health Resources and Services Administration (D28PE51008).

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