Management of Childhood Lead Poisoning:

Clinical Impact and Cost-Effectiveness

DEBORAH E. GLOTZER, MD, MPH, KENNETH A. FREEDBERG, MD, MSc, HOWARD BAUCHNER, MD

Objectives. No consensus exists regarding the preferred treatment of childhood lead poisoning. The authors used decision analysis to compare the clinical impacts and cost-effectiveness of four management strategies for childhood lead poisoning, and to investigate how effective chelation therapy must be in reducing neuropsychologic sequelae to warrant its use. *Methods.* The model was based on a 2-year-old child with moderate lead poisoning [blood lead level 1.21 to 1.88 μmol/L (25 to 39 μg/dL)]. The following strategies were compared: 1) no treatment; 2) EDTA provocation testing, followed by chelation if testing is positive (PROV); 3) penicillamine chelation with crossover to EDTA provocation testing if toxicity occurs (PCA); 4) EDTA provocation testing with crossover to penicillamine chelation if testing is negative (EDTA). *Results.* The EDTA and PCA strategies prevented 22.5% of the cases of reading disability and resulted in an increase of 1.02 quality-adjusted life years compared with no treatment. When the costs of outpatient EDTA testing and chelation are considered, the EDTA strategy is more cost-effective than the PCA strategy; when inpatient costs are considered, the PCA strategy becomes more cost-effective. When costs of remedial education are considered, all strategies are cost-saving compared with no treatment if chelation reduces the risk of lead-induced reading disability by more than 20%. *Conclusions.* Treatment strategies for childhood lead poisoning vary in clinical impact, cost, and cost-effectiveness. Chelation of the 1.4% of United States preschoolers whose blood lead levels are 1.21 μmol/L (25 μg/dL) or higher could prevent more than 45,000 cases of reading disability, and save more than $900 million per year in overall costs when the costs of remedial education are considered. *Key words*: lead poisoning; decision analysis; cost analysis; chelation. **(Med Decis Making 1995;15:13–24)**

Lead poisoning is one of the most common illnesses of childhood. It is generally agreed that reducing a child's exposure to lead is the cornerstone of effective therapy. Chelation for lead poisoning is often suggested for children whose venous blood lead levels are 1.21 μmol/L (25 μg/dL) or higher,[1] but this is not uniformly agreed upon. There is no consensus among lead toxicologists or pediatricians regarding the preferred treatment strategy for low-level lead poisoning in children. In a survey of pediatric lead-poisoning clinics, Glotzer and Bauchner determined that there is a wide range in the minimum blood lead levels for which chelation is recommended; 19% of survey respondents did not recommend chelation therapy for a child with a blood lead level below 1.93 μmol/L (40 μg/dL), and there is substantial variability in the treatment regimens recommended to reduce an elevated lead burden.[2]

Although it is well established that asymptomatic children with elevated lead burdens are at increased risk for neuropsychologic dysfunction,[3–11] including reading disability,[12] no definitive data exist regarding the effect of chelation with respect to lead-induced neurotoxicity. Chelation therapy with a variety of pharmacologic agents can be effective in reducing the blood lead level and the overall body lead burden, but existing data are inconclusive about which strategy is optimal. Lead-treatment strategies differ in the incidence and severity of adverse drug effects, inconvenience associated with treatment, treatment costs, and possibly, cognitive outcomes. However, the relative tradeoffs of these factors have not been investigated.

The United States Public Health Service has estimated that 1.4% (>200,000) of this nation's preschool children have blood levels of 1.21 μmol/L (25 μg/dL) or more.[13] Therefore, if there are significant differences

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Address correspondence and reprint requests to Dr. Glotzer: Department of Pediatrics, Boston City Hospital—Talbot 102, 818 Harrison Avenue, Boston, MA 02118.

in outcomes or costs among treatment strategies, the choice of a particular management strategy would have a substantial impact on the monetary and human resource costs to society. The objective of this study was to compare the clinical impacts and cost–effectiveness ratios of different management strategies for childhood lead poisoning, and to investigate how effective chelation therapy must be in reducing neuropsychologic sequelae to warrant its use.

These issues were explored using decision analysis.[14–16] Decision analysis is a systematic method of modeling clinical scenarios. It can be used to determine which management option is preferred for given a set of specified conditions, and can identify those variables within the model that are most important in decision making. It has a particularly useful role with respect to the management of childhood lead poisoning, because results of randomized controlled trials that address these issues will not be available for many years due the complexity and cost of performing the relevant studies and the lengthy follow-up required to collect the appropriate data.

Methods

STRUCTURE OF DECISION MODEL (FIGURE 1)

We used decision analysis to compare the following four management strategies: 1) no treatment (NO RX); 2) calcium disodium ethylenediamine tetraacetate (EDTA) provocation testing, followed by EDTA chelation if the test result is positive, or no treatment if the test result is negative (PROV); 3) penicillamine chelation with crossover to EDTA provocation testing if toxicity necessitates discontinuation of penicillamine or if there is an unsatisfactory response to penicillamine chelation (PCA); 4) EDTA provocation testing followed by EDTA chelation if the test result is positive, or penicillamine chelation if the test result is negative or if there is an unsatisfactory response to EDTA chelation (EDTA). The decision model was based on a prototypical 2-year-old child with newly-identified moderate lead poisoning [blood lead level 1.21 to 1.88 μmol/L (25 to 39 μg/dL)].

ABBREVIATIONS

EDTA = calcium disodium ethylenediamine tetraacetate
BAL = dimercaprol
QALE = quality-adjusted life expectancy
QALY = quality-adjusted life years
QOL = quality of life

The outcome measures evaluated in the model were: 1) direct medical costs; 2) cases of reading disability prevented; and, 3) quality-adjusted life expectancy (QALE).[17] The QALE is the average projected life expectancy adjusted for long-term disability, such as reading disability, as well as short-term toxicity and inconvenience associated with medical treatment. It equates the projected lifetime in a state of less than perfect health to the number of equivalent years of perfect health. The cost of remedial education was not included in the baseline analysis, but the effect of this cost was explored in a sensitivity analysis.

Baseline estimates used in the model were obtained from the medical literature when available. The quality-of-life (QOL) adjustment for reading disability was based on a survey of 13 pediatricians and pediatrics educators at Boston City Hospital. Estimates required for the model that were not available from the medical literature represent the authors' (DEG and HB) opinions.

Costs were obtained from the 1990 rate book of Children's Hospital, Boston, Massachusetts,[18] using ratebook charges and cost-to-charge ratios specific for each cost center. Costs, rather than charges, were used for this analysis, because costs more accurately reflect true resource use.[19] Future costs and quality-adjusted life years (QALYs) (QALY = unit of measure of QALE) were discounted at 5%.

Sensitivity analysis was used to explore the effects of changing variables over a range of clinically reasonable values. The variables and costs used in the model, the ranges tested in the sensitivity analyses, and the components of each cost estimate are listed in appendices A–C. The decision tree was constructed and evaluated using SMLTREE software[25] on an IBM-compatible personal computer.

MODEL ASSUMPTIONS

Chelation. The model was based on a 2-year-old child because the incidence of lead poisoning is highest in this group, and blood lead levels peak between 18 and 24 months of age. Chelation therapy is generally instituted as soon as possible once the need for chelation is established.

Although some children undergoing chelation therapy may receive more than one treatment course, in the baseline analysis we assumed that each child would be managed according to only one of the four strategies described and would not re-enter the decision model. We conducted sensitivity analyses to investigate the impact of an additional course of chelation.

We defined a course of EDTA or penicillamine chelation as successful if the blood lead level was reduced to below 1.21 μmol/L (25 μg/dL). Although it is not clear that a change in blood lead level is the best measure of chelator effectiveness, we elected to use it

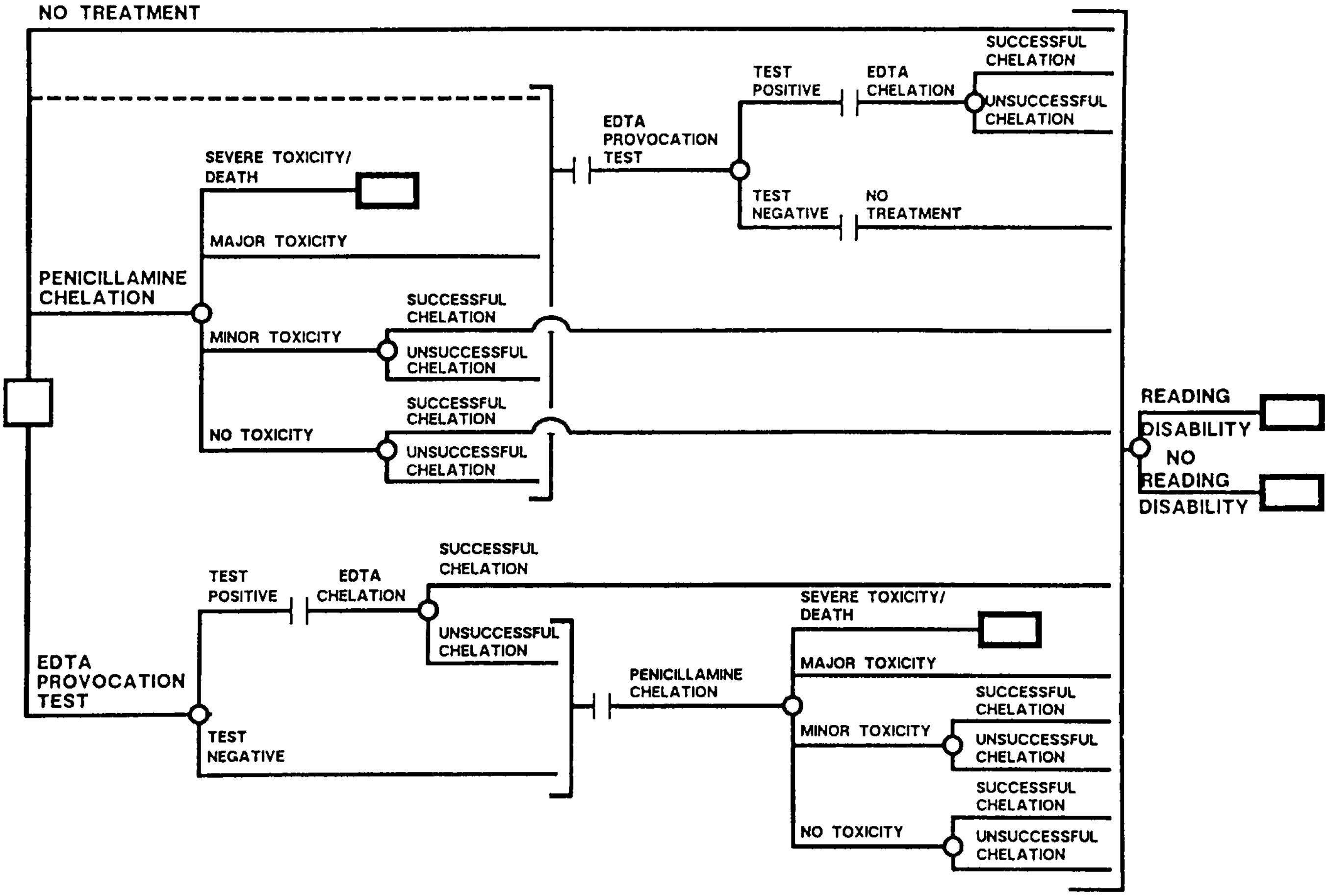

FIGURE 1. Decision model for treatment of childhood lead poisoning. See text for explanation of management strategies. Square nodes represent decisions; circular nodes represent chance occurrences; double lines represent label nodes; rectangular nodes represent outcomes; a bracket indicates that branches ending at the bracket enter subtrees depicted to the right of the bracket. A broken line indicates that the strategy begins with the EDTA provocation test (see text for description of all treatment strategies).

in this model because it is the parameter most frequently used to assess the outcome of chelation in clinical practice. A course of penicillamine chelation for low-level lead poisoning will successfully reduce the blood lead level 90% of the time.[22] There are no data that describe the effectiveness of EDTA in reducing the blood lead levels in children whose EDTA provocation test results are positive. However, a positive provocation test result is considered to indicate the subset of children most likely to respond to a full course of EDTA chelation. Therefore, in the baseline analysis we assumed that almost all children chelated with EDTA following a positive provocation test (98%) will have substantial declines in their blood lead levels.

Although prompt chelation with EDTA and dimercaprol (BAL) can substantially reduce the mortality and morbidity of symptomatic lead poisoning,[26] there are no controlled or conclusive data that indicate the long-term effect of reducing the lead burden in children with asymptomatic low-level poisoning. The premise that chelation confers a benefit with regard to neurodevelopment outcome is a critical assumption in this model. While there currently are no definitive data that address this issue, this premise forms the basis for pediatric lead-treatment programs. In the baseline analysis we assumed that in children whose blood lead levels were reduced by chelation or EDTA or penicillamine, the risk of developing reading disability as a result of lead poisoning decreased by 70% (appendix D). Because of the degree of uncertainty inherent in this assumption, a sensitivity analysis over the entire range of possible values (0–100%) was performed. We assumed that EDTA and penicillamine would have equal effects on the risk of reading disability for a similar decline in blood lead level, since there are no data about this parameter for either chelating agent investigated in our model. If clinical studies demonstrate that chelating agents differ in effectiveness with regard to neuropsychological sequelae, the impact of the difference could be examined in this model.

The baseline costs of EDTA provocation testing and chelation used in the model represent the estimated costs of outpatient management. EDTA can be safely administered by either the intramuscular or the intravenous route in low-level lead poisoning, and the route of administration is based on physician and parental preference, and sometimes insurance mandates. Although outpatient management is less labor- and resource-intensive and thus less costly than inpatient treatment, EDTA intramuscular injections are painful, and it can be difficult to achieve satisfactory hydration without intravenous access. Many pediatricians, therefore, prefer to administer EDTA by the intravenous route, which usually requires inpatient management. We investigated inpatient costs in the sensitivity analyses.

It was assumed that EDTA chelation would not cause toxicity sufficient to necessitate additional treatment or evaluation beyond a standard five-day treatment course with routine monitoring. Although EDTA is associated with serious adverse effects in patients who have lead encephalopathy and extremely high blood lead levels, this does not occur in patients with low-level lead poisoning.

Cost and QOL estimates associated with uncomplicated penicillamine chelation were based on a ten-week course of medication with weekly visits for the first two weeks of therapy and biweekly visits for the remainder of the treatment course (seven visits total). Additional costs and quality adjustments were added for penicillamine toxicity.

Neurodevelopmental outcome. Needleman's data on the incidence of reading disability in lead-poisoned children were based on dentin lead levels.[12] However, the high-lead-burden group had a mean blood lead level of 1.71 μmol/L (35.5 μg/dL),[27] which is in the range of lead exposure upon which the model is based. After controlling for confounding variables such as parental IQ, education, and socioeconomic status, the odds ratio of a lead-poisoned child's having reading disability compared with less exposed peers has a 95% confidence interval that ranges from 1.7 to 19.7[12] The range of these odds ratios was explored in a sensitivity analysis.

The QOL adjustment for reading disability is based on a scale of 0 to 1.00, with a state of perfect health without any disability valued at 1.00, and death valued at 0. Survey responses ranged from 0.50 to 0.98, with a mean value of 0.77 ± 0.14, which was applied to all future life years of reading disabled children. Reading disability is not an all-or-none phenomenon, but instead occurs along a continuum. The QOL adjustment used in this model represents the adjustment for an average disability. Sensitivity analysis was used to investigate the effect of varying the QOL adjustment from 0.50 to 1.00.

We assumed that all children with reading disability would receive a neuropsychologic evaluation, and would receive remedial education in grades 1–12. The costs of neuropsychologic evaluation were included in the baseline analysis. Remedial education costs were not included in the baseline analysis since the baseline model examined only direct medical costs. However, the effect of these costs was explored in a sensitivity analysis. The costs of remedial education used in this model represent average costs, and may under- or overestimate the educational costs for an individual child, depending on the extent of disability.

Results

BASELINE RESULTS (TABLE 1)

The average projected cost of the no-treatment strategy is $463 per child. The costs incurred from this strategy are from the costs of neuropsychologic evaluation in children who develop reading disability. The projected QALE for a lead-poisoned child who does not receive treatment is 18.25 years, which reflects both a reduced QALE due to reading disability and discounting of future life years (69.61 years = 62.55 QALYs = 18.25 discounted QALYs).

Table 1 • Baseline Results*

Strategy†	Cost ($)‡	QALE§ (years)	Probability of Reading Disability¶ (%)	Case of Reading Disability Prevented Compared with NO RX¶ (%)	Cost/QALY‖ Compared with NO RX ($/Year)	Cost/Case Prevented Compared with NO RX ($)
NO RX	463	18.25	44.1	—	—	—
PROV	786	18.65	35.3	8.8	804	3,688
EDTA	1,778	19.27	21.6	22.5	1,286	5,855
PCA	2,032	19.27	21.6	22.5	1,540	6,986

*Direct medical costs only, costs of remedial education not included.
†NO RX = no treatment; PROV = EDTA provocation test, with no treatment if test result is negative; EDTA = EDTA provocation test with crossover to penicillamine if test result is negative; PCA = penicillamine chelation with crossover to EDTA provocation test if toxicity occurs.
‡Rounded to nearest $1.
§QALE, quality-adjusted life expectancy, discounted at 5% per year, rounded to nearest 0.01 years.
¶Results rounded to nearest 0.1%.
‖QALY, quality-adjusted life year.

Table 2 • Incremental Cost–Effectiveness Ratios*†

Strategies Compared‡	Cost/QALY§ ($/year)	Cost/Case Prevented¶ ($)
PROV VS NO RX	804	3,688
EDTA VS PROV	1,597	7,238
PCA VS EDTA	EDTA dominates‖	EDTA dominates

*Direct medical costs only, costs of remedial education not included.
†Incremental cost–effectiveness ratios indicate the additional cost per additional unit of benefit (QALY or case prevented).
‡NO RX = no treatment; PROV = EDTA provocation test, with no treatment if test result is negative; EDTA = EDTA provocation test with crossover to penicillamine if test result is negative; PCA = penicillamine chelation with crossover to EDTA provocation test if toxicity occurs.
§QALY = quality-adjusted life year, discounted at 5% per year.
¶Case prevented: case of reading disability prevented.
‖EDTA dominates: more expensive strategy (PCA) is not more effective.

The provocation-treatment strategy costs $786 per child, yields 18.65 QALYs, and will prevent 8.8% of cases of reading disability compared with no treatment. This strategy will cost $804 for each additional QALY gained and $3,688 per case of reading disability prevented compared with no treatment.

The EDTA and penicillamine strategies result in equal QALEs (19.27 years), and will prevent the same number of reading disability cases compared with no treatment (22.5%). However, under baseline conditions the penicillamine strategy costs more than the EDTA strategy, so that the cost per case of reading disability prevented compared with no treatment is higher with the penicillamine strategy ($6,986) than with the EDTA strategy ($5,855). Therefore, under baseline conditions the penicillamine strategy is not cost-effective compared with the EDTA strategy.

INCREMENTAL COST–EFFECTIVENESS (TABLE 2)

Incremental cost–effectiveness ratios are shown in table 2. These ratios indicate the additional cost incurred for each additional unit of benefit (QALY or case of reading disability prevented) realized by using a more costly, but more effective, strategy. They can be used to determine the most appropriate allocation of limited financial resources. Although the no-treatment strategy is the least expensive strategy in terms of average costs, the projected QALE and the number of cases of reading disability prevented using each of the other strategies are greater. Management with the EDTA strategy increases the QALE by 0.62 years [(19.27 QALYs) − (18.65 QALYs)] compared with the provocation test strategy, and will prevent an additional 13.7% [(22.5%) − (8.8%)] of cases of reading disability at a cost of $1,597 per additional QALY gained, and $7,238 per additional case of disability prevented. Under baseline conditions the penicillamine strategy is dominated by the EDTA strategy, that is, the penicillamine strategy is more expensive but not more effective.

SENSITIVITY ANALYSES

Quality-of-life adjustments. The QOL adjustment for reading disability has a substantial impact on the overall QALE. If reading disability has no deleterious effect on the QOL (as it relates to neuropsychologic outcome), then any intervention for lead poisoning will negatively impact the QOL because of the inconvenience and toxicity associated with treatment, and the no-treatment strategy would be preferred over any other strategy. However, because lead poisoning generally affects young children, even modest reductions in the QOL can have a significant impact on the projected QALE. Table 3 shows the incremental cost–effectiveness ratios for different treatment strategies as the QOL adjustment for reading disability is varied. So long as

Table 3 • Sensitivity Analysis: Quality-of-life Adjustment for Reading Disability*

QOL Adjustment† (Baseline = 0.77)	Strategies‡ Listed in Order of Increasing Cost)	Incremental cost–effectiveness ratio§ ($/QALY¶)
0.90	NO RX	—
	PROV	1,896
	EDTA	3,827
	PCA	EDTA dominates‖
0.95	NO RX	—
	PROV	3,968
	EDTA	8,267
	PCA	EDTA dominates
0.96	NO RX	—
	PROV	5,078
	EDTA	10,763
	PCA	EDTA dominates
0.97	NO RX	—
	PROV	7,048
	EDTA	15,421
	PCA	EDTA dominates
0.98	NO RX	—
	PROV	11,519
	EDTA	27,182
	PCA	EDTA dominates
0.99	NO RX	—
	PROV	31,502
	EDTA	114,572
	PCA	EDTA dominates

*Direct medical costs only, costs of remedial education not considered.
†QOL adjustment = quality-of-life adjustment for reading disability.
‡NO RX = no treatment; PROV = EDTA provocation test, with no treatment if test result is negative; EDTA = EDTA provocation test with crossover to penicillamine if test result is negative; PCA = pencillamine chelation with crossover to EDTA provocation test if toxicity occurs.
§Incremental cost–effectiveness ratio indicates the additional cost per additional quality-adjusted life year gained using a more costly and more effective strategy.
¶$/QALY: cost per quality-adjusted life year, discounted at 5% per year.
‖EDTA dominates: more expensive strategy (PCA) is not more effective.

Table 4 • Sensitivity Analysis

Variable (Baseline Value, Value Tested)	Strategies*	Cost ($)	Cost/Case Prevented ($)†	Incremental Cost–Effectiveness Ratio‡ ($/Case Prevented)
Cost: remedial education ($0, $27,614)	EDTA	7,748	−21,763§	—
	PCA	8,001	−20,633	Dominated¶
	PROV	10,540	−23,923	Dominated
	NO RX	12,636	—	Dominated
Cost: penicillamine chelation ($1,632, $800)	NO RX	463	—	—
	PROV	786	3,688	Extended dominance‖
	PCA	1,200	3,281	3,281
	EDTA	1,232	3,421	Dominated
Cost: EDTA provocation test (238, $600)	NO RX	463	—	—
	PROV	1,148	7,821	Extended dominance
	PCA	2,099	7,280	7,280
	EDTA	2,140	7,466	Dominated
Cost: EDTA chelation ($506, $2500)	NO RX	463	—	—
	PROV	1,484	11,656	Extended dominance
	PCA	2,160	7,553	7,553
	EDTA	2,476	8,962	Dominated
Probability of positive EDTA provocation test (355, 105)	NO RX	463	—	—
	PROV	726	10,481	Extended dominance
	PCA	2,021	7,308	7,308
	EDTA	2,087	7,618	Dominated

*Strategies listed in order of increasing cost: NO RX = no treatment; PROV = EDTA provocation test, with no treatment if test result is negative; EDTA = EDTA provocation test with crossover to penicillamine if test result is negative; PCA = penicillamine chelation with crossover to EDTA provocation test if toxicity occurs.

†Compared with no-treatment strategy.

‡Incremental cost–effectiveness ratios indicate the additional cost per additional case of reading disability prevented using a more costly and more effective strategy.

§Negative numbers indicate that EDTA, PCA, and PROV strategies are cost-saving when costs of remedial education are included.

¶Dominated indicates that strategy is not cost-effective compared with the next less expensive strategy because of higher costs and equal or lower effectiveness.

‖Extended dominance indicates that strategy is not cost-effective compared with next more expensive strategy because it has a higher incremental cost–effectiveness ratio. The more expensive strategy is associated with more effectiveness for a fixed cost.

the QOL adjustment for reading disability is 0.97 or less (1.00 = state of perfect health, without disability), the cost–effectiveness ratio for medical intervention remains below $20,000 per QALY gained, a ratio that is considered reasonable in many health policy analyses.[28] Thus, although the QOL adjustment for reading disability was based on a survey of a small number of physicians, and is therefore somewhat imprecise, the model is relatively insensitive to changes in this variable.

The results are not substantially affected by changes in the QOL adjustments for all medical interventions, including those estimated by the authors.

Educational costs. The added cost of remedial education has an important effect on the results of our decision model. Raphael et al. have reported that the mean educational expenditure for learning-disabled students is 1.8 times greater than the mean educational expenditure for students receiving regular education,[24] for an additional annual cost of $3,607 per learning-disabled child.[20] The projected additional cost of remedial education from grades 1–12 is $27,614 in present value dollars discounted at 5% per year.

Under baseline conditions (table 1) and most conditions tested in the sensitivity analyses (table 4), the cost per case of reading disability prevented by each strategy compared with no treatment is far less than the cost of remedial education. This indicates that when educational costs are included in this model, the provocation test, EDTA, and penicillamine strategies are all cost-saving compared with no treatment. The no-treatment strategy, which is the least effective strategy, becomes the most expensive strategy when the cost of remedial education is considered. The EDTA strategy dominates all other strategies because it is the least costly and most effective strategy.

Medical costs. The model is also sensitive to changes in the costs of penicillamine chelation, EDTA provocation testing, and EDTA chelation (table 4). The baseline cost estimate of a course of penicillamine chelation is $1,632. The cost to administer therapy probably would be lower if care were given in a non-hospital setting. If the cost of a course of penicillamine chelation is $800, the EDTA strategy becomes more costly, but not more effective, than the penicillamine strategy, and therefore is dominated by the less expensive penicillamine strategy. The penicillamine strategy is also more cost-effective than the provocation test strategy when the cost of penicillamine chelation is reduced.

When higher costs of inpatient EDTA provocation testing ($600) and chelation ($2,500) are considered, both the provocation test and EDTA strategies are not cost-effective compared with the penicillamine strategy.

The results are not substantially affected by changes in the costs of penicillamine toxicity (minor, major, and severe) or the cost of evaluation for a child with a reading disability.

The costs used in this model represent costs from a not-for-profit academic teaching institution in Boston, Massachusetts. While these costs are likely to be higher than national averages, the baseline estimates for all strategies tested represent outpatient costs, and therefore it is unlikely that the high cost of medical care in Boston favored any one strategy over another.

Additional chelation. The baseline model assumes that each child will receive only a single course of chelation. It is possible that some children will require an additional course of chelation to achieve a successful chelation result. However, even if as many as 50% of children undergo a second course of chelation, the relative costs and the cost–effectiveness ratios of the strategies do not change.

EDTA provocation testing. In the baseline analysis we assumed that EDTA provocation test would be positive 35% of the time.[23] If only 10% of tested children have positive provocation test results, as found by Weinberger et al.,[29] the penicillamine strategy becomes more cost-effective than the EDTA or provocation-test strategies.

Effectiveness of chelation in reducing risk of reading disability. Changes in the effectiveness of chelation in reducing the risk of lead-induced reading disability affect the cost–effectiveness ratios of different strategies (fig. 2). We determined the minimum chelation effectiveness at which the cost of remedial education exceeds the cost of medical management. Assuming that chelation reduces the risk of developing reading disability by 20% or more, the estimated cost of remedial education for a reading-disabled, lead-poisoned child ($27,614) exceeds the cost of preventing the reading disability when the EDTA strategy is compared with the provocation-test strategy. Therefore, the EDTA strategy is cost-saving compared with all other strategies when direct medical and educational costs are considered. If chelation effectiveness is between 12% and 20%, the cost of remedial education is greater than the cost of preventing a case of reading disability with the provocative-test strategy but not the EDTA strategy. For all estimates of chelation effectiveness, the risk of lead-induced reading disability is lower for a child managed with the EDTA strategy than with the provocation-test strategy. However, the incremental cost of preventing disability with the EDTA strategy compared with the provocation-test strategy becomes substantially higher as the effectiveness of chelation decreases because of the lower cost of the provocation-test strategy. The costs of medical treatment with all treatment strategies are greater than the costs of remedial education only if chelation is less than 12% effective in reducing the risk of reading disability.

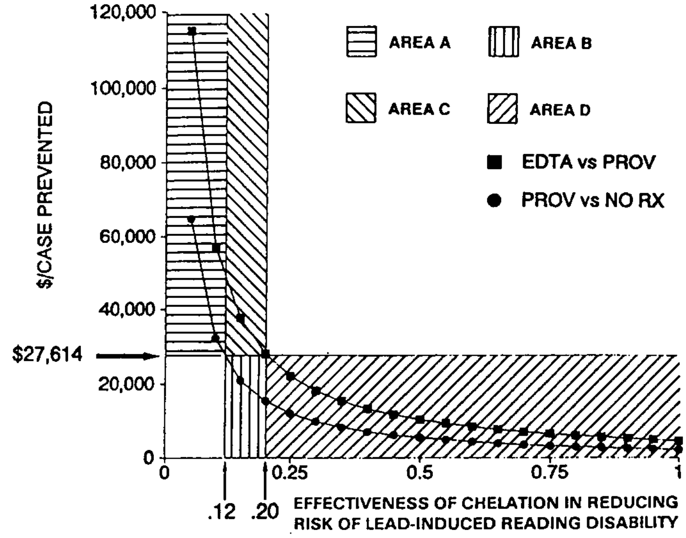

FIGURE 2. The impacts of changes in the effectiveness of chelation in reducing the risk of lead-induced reading disability on the incremental cost–effectiveness of the EDTA and provocation test strategies. The cost of medical treatment exceeds the cost of remedial education ($27,614) only if chelation reduces the risk of reading disability by less than 12% (area A). The cost of preventing lead-induced reading disability with the EDTA strategy exceeds the cost of remedial education if the effectiveness of chelation is between 12% and 20% (area B). If chelation effectiveness is between 12% and 20%, the cost of preventing a case of reading disability with the provocation test strategy is less than the cost of remedial education (area C). If chelation effectiveness is 20% or greater, the EDTA strategy is cost-saving compared with all other strategies if the costs of remedial education are considered (area D).

Risk of reading disability in lead-poisoned children. If the risk of reading disability is only 1.7 times greater in lead-poisoned children, then the cost of preventing a case of reading disability exceeds the cost of remedial education services for all strategies. However, if the risk of having reading disability is 1.8 or greater, the medical costs incurred by the provocation-test strategy to prevent reading disability are less than the cost of remedial education. The minimum odds ratios that make the EDTA and penicillamine strategies cost-saving compared with no treatment are 2.2 and 2.4, respectively.

Other variables. Changes in the estimated prevalence of reading disability is non-poisoned children, in the QOL adjustments for all medical interventions (including the authors' estimates), in the probability of penicillamine-related toxicity, and in the discount rate, do not substantially affect the results.

Discussion

The management (and many other aspects) of childhood lead poisoning is a controversial topic. Much of this controversy arises from gaps in our current understanding of this disease. There is a clear need for better data regarding the impact of chelation of children with lead poisoning. However, such data do not exist at present, and there are significant limitations, such as cost and length of follow-up, in terms of conducting the relevant studies to compile the data. In the absence of such data, decision analysis can provide preliminary answers to important questions: How effective is chelation in reducing the risk of adverse sequelae of lead poisoning? Are there differences in available treatments to clearly recommend one approach over another?

This analysis demonstrates that different strategies for the treatment of childhood lead poisoning vary in direct medical costs and cost–effectiveness. Under the baseline conditions tested, the EDTA and penicillamine strategies were substantially more effective than the provocation-test and no-treatment strategies in terms of cases of reading disability prevented and in quality-adjusted life years gained. Although these strategies are more expensive than the less effective strategies, they appear to be cost-saving when the cost of remedial education is considered. Even if remedial education costs are not considered, the more expensive and more effective chelation strategies are at least as cost-effective as many medical interventions that are generally accepted for widespread use, including neonatal intensive care ($36,250 per QALY gained[30]), screening for sickle cell disease in the general population of newborn infants ($41,436 per life saved[31]), or the treatment of hypertension in adults ($13,640 per year of life saved[32]) (all costs were converted to 1990 dollars using the medical care component of the Consumer Price Index[20]).

Chelation of asymptomatic low-level lead poisoning is often recommended in an attempt to prevent lead-induced neurotoxicity, although there are no definitive data indicating the effectiveness of chelation in preventing neuropsychologic morbidity. However, previously we reported that 48% to 79% of lead-poisoning clinic directors, practicing in areas where childhood lead poisoning is most prevalent, recommend chelation for children whose blood lead levels are 1.21 to 1.88 μmol/L (25 to 39 μg/dL).[2] This indicates that although there are differing positions on this issue, the consensus view is that chelation is warranted for such children. That chelation may decrease the risk of neuropsychologic sequelae is a critical assumption in our model. The results of this analysis suggest that chelation would not have to be very effective to be cost-saving. Even if chelation reduced the risk of lead-induced disability by only 12% to 20%, depending on treatment strategy, it would be cost-saving.

The costs and cost–effectiveness ratios of the EDTA and penicillamine treatment strategies relative to each other are greatly affected by the costs of EDTA provocation testing and chelation. The additional cost of inpatient EDTA chelation increases the cost and cost per case of reading disability prevented with the EDTA strategy by 39% and 53%, respectively, whereas the cost and cost per case prevented increase by only 6% and 8%, respectively, with the penicillamine strategy. When EDTA provocation testing or chelation is administered in an impatient setting, initial chelation with penicillamine is less costly and more cost-effective than initial management with EDTA. Therefore, based on the assumptions used in this model, for the majority of lead-poisoned children initial management with outpatient penicillamine may be the preferred treatment strategy.

Although toxic side effects have been reported to occur in as many as one-third of patients given penicillamine, most side effects are minor and do not necessitate discontinuation of therapy.[22] This analysis suggests that the inconvenience of treatment, monitoring associated with treatment, and adverse effects of treatment are not sufficiently great to avoid the use of penicillamine in children for whom chelation is warranted.

Lead-poisoned children may have coexisting conditions that complicate the management of their lead burdens. For some children, such as those who have leukopenia or thrombocytopenia, chelation with penicillamine may be contraindicated, and the provocation-test strategy would be the management strategy of choice.

This model does not address the treatment of children with high initial blood lead levels [≥1.93 μmol/L (40 μg/dL)], children with elevated lead burdens but with blood lead levels below 1.21 μmol/L (25 μg/dL), or children with repeated low-level poisonings who undergo multiple courses of therapy. The implications of this model for children in these categories are less clear. A child's risk of experiencing cognitive deficits is generally thought to be related to the duration of poisoning, the age of the child when initially poisoned, and the extent of poisoning. However, there are no data regarding the effects of poisoning at various ages or for different durations. Therefore, this model was based on the only available published data that relate the extent of elevated lead burden to the risk of neuropsychologic sequelae. The possible confounding effects of coexisting iron-deficiency anemia and other medical and social conditions were not explicitly considered in this model. However, the adjusted odds ratio of reading disability in lead-poisoned children used in the model controls for some of these potentially confounding variables.[12]

We used the incidence of reading disability as an outcome measure in the model because, although there is a range of severity of reading disability in affected children, it is a discrete endpoint. We elected to use incidence of reading disability rather than IQ decrements as an outcome measure in this model because reading disability represents a functional outcome, and the cost of remedial education is known.

In this analysis the quality adjustment for reading disability was obtained with a visual analog scale. Although other scaling methods such as the standard reference gamble or the time trade-off method generally result in higher utilities than a rating scale, it is not clear that these other methods reflect patient preferences more accurately.[33–35] Sensitivity analysis indicates that the QOL adjustment for a child with reading disability must exceed 0.97 for the cost–effectiveness ratio for medical intervention to exceed $20,000 per QALY. Therefore, it is unlikely that the results of this model would change substantially if a different scaling method were used.

Although initial reports regarding the recently approved orally active chelating agent, 2,3-dimercaptosuccinic acid, are encouraging, this drug was not included in the model because current safety and efficacy data for its use in children with low-level poisonings are insufficient to permit analysis at this time. The strategies considered in the model represent the most frequently used management strategies used in childhood lead-poisoning clinics,[2] and those for which data are available to support decision analysis. Other treatment strategies may be reasonable as well. Empiric EDTA treatment was not considered in this model because this method of treatment is recommended less than 10% of the time for children whose blood lead levels are less than 1.93 μmol/L (40 μg/dL).[2] Furthermore, empiric EDTA chelation is less expensive than management with the EDTA provocation test only if the probability of a positive provocation test is 53% or greater. Published studies indicate that the EDTA provocation is positive 9 to 35% of the time for children whose blood lead levels are less than 1.93 μmol/L (40 μg/dL),[23,28,36] and therefore empiric EDTA chelation would not be a cost-effective strategy.

We did not consider the impacts and cost–effectiveness ratios of educational, nutritional, and environmental interventions for the treatment of childhood lead poisoning. Clearly, chelation must be considered as an adjunct and not a substitute for other methods of limiting and reducing a child's exposure to lead. With the exception of household lead paint abatement, these interventions are "low-tech" and inexpensive. Dust-control measures have been shown to significantly reduce children's lead exposure, blood lead levels, and the need for chelation.[37] A decision analysis that investigated the financial benefits of preventing lead exposure of children via prophylactic abatement of lead-based paint indicated that abatement activities can result in substantial overall cost savings.[38] However, at least for the near future, children will continue to become lead-poisoned, and the lead burdens of a substantial fraction of these children will not be effectively reduced with environmental and nutritional interventions alone.

There is no consensus among physicians who frequently treat lead-poisoned children about the preferred therapeutic approach, and it appears that a substantial fraction of children who have blood lead levels above 1.21 μmol/L (25 μg/dL) do not receive chelation therapy.[2] If chelation leads to an improved quality-adjusted life expectancy and overall cost savings, as suggested by this model, chelation should be strongly considered for children with elevated blood lead burdens above 1.21 μmol/L (25 μg/dL). The best available current estimates indicate that 1.4% of United States preschoolers (over 200,000 children) have blood lead levels above 1.21 μmol/L (25 μg/dL).[13] Our model suggests that EDTA or penicillamine chelation of these children could prevent more than 45,000 cases of reading disability annually, and save more than $900 million per year in overall costs when both medical and remedial education costs are considered. We did not consider the impact of indirect costs of lead poisoning and its treatment in this model. Lead poisoning during childhood is likely to decrease overall future lifetime earnings through reductions in wage rate and labor force participation.[38] Therefore, the results of this analysis represent a conservative estimate of the financial benefits of chelation therapy.

The results of this decision model must be approached with some caution, and should not be viewed simply as a prescription for the treatment of lead-poisoned children. Rather, this analysis demonstrates that data regarding the cognitive outcome of children who receive chelation for an elevated lead burden are needed. 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. Based on this analysis, chelation of these children should be strongly considered.

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APPENDIX A

Baseline Estimates in the Model, and Ranges Tested in Sensitivity Analysis

Variable	Baseline	Range	Reference
Life expectancy of 2-year-old child (weighted for racial distribution of lead poisoning)	69.61 years	—	Census[20]
QOL* adjustment for reading disability	0.77/year	0.5–1/year	†
Discount rate	5%	0–10%	Weinstein and Fineburg[15]
Rate of reading disability in general population	7.6%	1–15%	Shaywitz et al.[21]
Odds ratio of reading disability in lead-poisoned children	5.8	1–13	Needleman et al.[12]
Effectiveness of penicillamine chelation in reducing neuropsychologic sequelae	70%	0–100%	‡
Effectiveness of EDTA chelation in reducing neuropsychologic sequelae	70%	0–100%	‡
Probability that penicillamine chelation will reduce blood lead level	90%	50–100%	Shannon et al.[22]
Probability that EDTA chelation will reduce blood lead level when provocation test is positive	98%	50–100%	‡
Probability of positive EDTA provocation test	35%	5–50%	Markowitz and Rosen[23]
Probability of penicillamine toxicity	33%	0–70%	Shannon et al.[22]
Minor toxicity	72%	50–100%	Shannon et al.[22]
Major toxicity	28%	0–50%	Shannon et al.
Severe toxicity/death	0.0003%	0–0.003%	‡
QOL* adjustment			
EDTA provocation test	1 day	0–2 days	‡
EDTA chelation	5 days	0–10 days	‡
Pencillamine chelation	10.5 days	0–20 days	‡
Penicillamine, minor toxicity	0.25 days	0–2.5 days	‡
Penicillamine, major toxicity	0.75 days	0–7 days	‡
Penicillamine severe toxicity/death	69.61 years	—	‡
Cost			
EDTA provocation test (outpatient)	$238	$100–1,000	Children's Hospital Rate Book[18]
EDTA chelation (outpatient)	$506	$200–4,000	Children's Hospital Rate Book[18]
Penicillamine chelation	$1,632	$200–3,600	Children's Hospital Rate Book[18]
Penicillamine minor toxicity	$188	$100–2,000	Children's Hospital Rate Book[18]
Penicillamine major toxicity	$566	$100–5,000	Children's Hospital Rate Book[18]
Penicillamine severe toxicity/death	$3,896	$1,000–30,000	Children's Hospital Rate Book[18]
Evaluation for reading disability	$1,051	$0–3,000	Children's Hospital Rate Book[18]
Remedial education/year	$0/year	$0–7,000	Census[20]; Raphael et al.[24]

*QOL = quality of life.
†No data available in the literature; based on survey of 13 pediatricians and pediatrics educators.
‡No data available in the literature; estimates are the authors'.

APPENDIX B

Component Costs Used in the Model

Laboratory and diagnostic tests/procedures	
Blood lead level	$ 16
Erythrocyte protoporphyrin level	$ 10
Complete blood count, with differential	$ 24
Electrolytes (blood)	$ 14
Urinalysis	$ 15
Urine lead level	$ 23
Venipuncture	$ 3
Arterial blood gas	$ 11
Electrolytes (urine)	4 20
Chest x-ray	$ 85

Hospitalizations and outpatient visits	
EDTA provocation test (outpatient)	$ 200
EDTA chelation (five-day, outpatient)	$ 373
Outpatient visit	
Initial	$ 164
Follow-up	$ 133
Neuropsychological evaluation	$1,051
Intensive care unit (per day)	$1,583
Respiratory therapy (per day)	$ 25
Assisted ventilation (per day)	$ 86

Medication: Penicillamine (10 week course) $ 95