Setting the Optimal Erythrocyte Protoporphyrin Screening Decision Threshold for Lead Poisoning: A Decision Analytic Approach

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ABSTRACT. Erythrocyte protoporphyrin (EP) was introduced in the 1970s as an inexpensive screening test for lead poisoning. As greater knowledge of lead poisoning has accumulated, the recommended EP level at which further evaluation for lead poisoning should be initiated has been lowered from ≥50 μg/dL to ≥35 μg/dL. The purpose of this study was to evaluate the utility of this EP threshold. A receiver operator characteristic curve was constructed to assess the relationship between the true-positive rate and false-positive rate of EP at various decision thresholds. The receiver operator characteristic curve was constructed with data from the second National Health and Nutrition Examination Survey from 1976 to 1980, which included 2673 children 6 years of age or younger who had both blood lead and EP level determinations. Decision analysis was then used to determine the optimal EP decision threshold for detecting a blood lead level ≥25 μg/dL. The receiver operator characteristic curve demonstrated that EP is a poor predictor of a blood lead level ≥25 μg/dL. At the currently recommended EP decision threshold of 35 μg/dL, the true-positive rates and false-positive rates of EP are 0.23 and 0.04, respectively. As a result of the inadequate performance of EP screening for lead poisoning, when the prevalence of lead poisoning is greater than 8%, there is no EP decision threshold that optimizes the relationship between the cost of screening normal children and the benefit of detecting lead-poisoned children. Erythrocyte protoporphyrin measurement is not sufficiently sensitive to be recommended uniformly as a screening test for lead poisoning. *Pediatrics* 1991;88:121–131; *cost-benefit analysis, decision analysis, erythrocyte protoporphyrin, lead poisoning, receiver operator characteristic curve.*

ABBREVIATIONS. CDC, Centers for Disease Control; EP, erythrocyte protoporphyrin; ROC, receiver operator characteristic; NHANES II, second National Health and Nutrition Examination Survey.

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As a greater understanding of the physiological and neuropsychological effects of lead has evolved, the definition of lead poisoning has changed. In 1971 the American Academy of Pediatrics recommended that lead poisoning be defined as two blood lead levels ≥50 μg/dL.[1] In 1978, the Centers for Disease Control (CDC) recommended that the definition of an elevated blood lead level be reduced to ≥30 μg/dL, and in 1985[2] their recommendation changed such that the definition was reduced to ≥25 μg/dL. The recent decision to decrease the blood lead level that defines lead poisoning was in response to studies that demonstrated the adverse health effects of moderately high blood lead levels (blood lead levels <40 μg/dL).[3–6]

The accurate measurement of lead in the blood is labor-intensive. Consequently, lead measurements have not routinely been used to screen for lead poisoning. The measurement of erythrocyte protoporphyrin (EP) in the blood has been the primary screening technique for lead poisoning because it is easy to perform and inexpensive. At a blood lead level ≥40 μg/dL, the EP level rises exponentially.[7] Thus, an EP level greater than a specified level serves as an index of excessive lead exposure and is the basis for further evaluation for lead poisoning.

In addition to the new definition of an abnormal blood lead level, the EP decision threshold, the EP level at which further diagnostic work should be done, has recently been lowered from ≥50 μg/dL to ≥35 μg/dL.[2] The reason for reducing the threshold is to identify lead poisoning in more asymptomatic

children. The American Academy of Pediatrics has stated "as the evidence of the low-dose toxicity of lead continues to develop, these definitions will be lowered still further." [8] Neither the CDC nor the Academy addressed the effectiveness of EP screening for lead toxicity at the new decision threshold value.

A measure of a good screening test is its ability to detect individuals with the disease (sensitivity), as well as to identify individuals without the disease (specificity). Setting the EP decision threshold presents the dilemma of a trade-off between sensitivity and specificity. The lower the decision threshold, the higher is the sensitivity and the lower is the specificity. On the other hand, at a higher decision threshold, the sensitivity is lower and the specificity is higher. A receiver operator characteristic (ROC) curve is a graphic depiction of the relationship between sensitivity and specificity. The curve depicts the relationship between the true-positive rate (sensitivity) and false-positive rate (1-specificity) over a range of decision thresholds.

The decision threshold that maximizes the expected utility of testing takes into account the prevalence of the disease, as well as the ratio of the cost to the benefit of screening.[9, 10] To establish the optimal decision threshold requires the prevalence of the disease; a ROC curve for the test; and an assessment of the costs associated with the four possible outcomes of the test: true-positive result, false-positive result, true-negative result, and false-negative result.

The purpose of our study is to assess the performance characteristics of EP for lead poisoning screening and to determine the optimal decision threshold for EP screening for lead poisoning in children 6 years of age or younger.

METHODS

Sample Design

We used the second National Health and Nutrition Examination Survey (NHANES II) conducted by the National Center for Health Statistics from 1976 to 1980 as our sample population. NHANES II was a cross-sectional study of the United States population aged 6 months to 74 years of age.[11] A total of 27 801 individuals from 64 sampling areas were selected as a weighted representation of the national population. As part of the survey, 2673 children, 6 years of age or younger, had both a blood lead and an EP level determination.

Definition of Lead Poisoning

We defined lead poisoning as a blood lead level ≥25 μg/dL. This definition is based on a modified version of the CDC's recommendation for lead poisoning, a blood lead level ≥25 μg/dL and an EP level ≥35 μg/dL. We were unable to use EP as part of our definition for lead poisoning because EP is the screening test being evaluated. Of the 2673 children, 313 had a blood lead level ≥25 μg/dL (prevalence, 12%).

Severity of Lead Poisoning

To assess the indirect and direct costs of lead poisoning, we used the CDC's recommendations for classifying children with lead toxicity to place each child with lead poisoning into either class II (blood lead level ≥25 μg/dL and EP level >35 μg/dL and <109 μg/dL), class III (blood lead level ≥25 μg/dL and <50 μg/dL with an EP level ≥110 μg/dL or blood lead level ≥50 μg/dL and <69 μg/dL with an EP level ≥35 μg/dL and <250 μg/dL), or class IV (blood lead level ≥50 μg/dL and <69 μg/dL with an EP level ≥250 μg/dL or blood lead level ≥70 μg/dL with an EP level ≥110 μg/dL).[2] The percentage of the 313 NHANES II children with lead poisoning in each of the three classes were 86.3%, class II; 10.9%, class III; and 2.8%, class IV. Children in class III who were identified as having lead poisoning were further subdivided as having a positive or negative provocative chelation challenge. Based on the data from Graef,[12] an estimated 40% of the children in class III will have a positive provocative chelation challenge, defined as the lead excretion ratio (the total urinary excretion of lead divided by the amount of disodium calcium-edetate given) exceeding 0.6.[2]

Inasmuch as prognosis depends on the presence of symptoms, class IV was subdivided into children with and without symptoms of lead toxicity. We were unaware of any publication that provides the percentage of children in class IV that were with and without symptoms; therefore, we estimated that approximately 80% of the children with class IV lead poisoning will be asymptomatic and 20% will have symptoms of lead toxicity.

Laboratory Analysis

The blood lead and EP levels were determined by the Clinical Chemistry Division, Center for Environmental Health of the CDC. The blood lead evaluation was done by atomic absorption spectrophotometry using a modified Delves cup micromethod.[13] Specimens were analyzed in duplicate and the average of the two results were used.[13] The

EP determination was done using the modified ethyl acetic acid extraction method.[13] Quality control measures for both procedures are described elsewhere.[13]

Limitations of the Data

Not all participants in the NHANES II survey had a blood lead level determination. Fifty-one percent of the children from 6 months through 5 years of age and 28.6% of those 6 through 17 years of age did not have a blood lead determination.[14] Individuals with a blood lead determination have been previously compared to the total sampled population. The subsample with a blood lead determination was found to be the same as the subsample without a blood lead determination in race, sex, annual family income, and degree of urbanization of residence.[15] Erythrocyte protoporphyrin level was not measured in 0.6% of the persons with a blood lead determination.[15]

Receiver Operator Characteristic Curve

The ROC curve was generated from the data of NHANES II survey. The data set for the survey is available in electronic form and is in the public domain. The sample consisted of 2673 children 6 years of age or younger who had a blood lead and EP determination. The ROC curve was generated by determining the true-positive rate and false-positive rate of EP at selected EP decision thresholds. The true-positive rate is the number of children in the sample with a blood lead level ≥ 25 μg/dL and an EP value greater than or equal to the decision threshold divided by the number of children with a blood lead level ≥ 25 μg/dL. The false-positive rate is the number of children with a blood lead level <25 μg/dL and an EP level greater than or equal to the decision threshold divided by the number of children with a blood lead level <25 μg/dL.

A series of EP decision thresholds (10, 15, 20, 25, 35, and 50 μg/dL) were chosen and the true-positive rate and the false-positive rate of each was determined. The true-positive rate and false-positive rate for each of the six EP decision thresholds were plotted as an ROC curve, with the y axis as the true-positive rate and the x axis as the false-positive rate. The best-fit ROC curve was generated by the MacROC computer program using the six points from each decision threshold. (This analysis was performed by John Swets, PhD; personal communication.) Table 1 shows the corresponding true-positive rate and false-positive rate (± 1 SD) for each decision threshold. Figure 1 shows the ROC curve.

Model for Determining the Optimal Decision Threshold

The optimal decision threshold was chosen by determining the point on the ROC curve where the expected utility of using the test was maximized.[9] The optimal decision threshold takes into account the prevalence of lead poisoning in the screening population and the ratio of the cost of using the test in normal children to the benefit of using the test in children with lead poisoning (see Appendix for equation 1).

To estimate cost and benefits, we needed to represent all outcomes of lead poisoning screening. Each of the four outcomes of the test—true-positive, true-negative, false-positive, or false-negative—has a cost. We calculated the total cost in dollars of each outcome as the sum of its direct cost and its indirect cost. The direct cost was the cost of medical care that each child would receive as a result of lead screening. The indirect cost was the reduction in future earnings of a child who has either mental retardation or a learning disability secondary to lead poisoning.

We used a tree representation to show the outcomes of a true-positive and false-negative EP result. As a result, we were able to calculate the expected indirect and direct cost of illness for a true-positive and false-negative test result. The expected cost of both a true-positive and false-negative depends on the interrelationship of several factors: the class of lead poisoning, the sequence of events for each class of lead poisoning, and the associated probabilities. Figure 2 shows the tree representation of a true-positive and false-negative test result. The only difference between the two results is that the events after a false-negative result do not include the provocative chelation test in class III.

The probability that sequelae will develop in a child with lead poisoning is difficult to assess. We used the work of Berwick and Komaroff,[16] who pooled the available studies and used expert opinion to estimate the probability, for each class of lead toxicity, that a child will become mentally retarded or learning disabled. The effectiveness of lead screening in preventing the sequelae of lead poisoning is unknown. We used Berwick and Komaroff's[16] estimate that lead poisoning programs are 50% effective in preventing mental retardation and learning disabilities. Table 2 lists, for both a true-positive and false-negative screening result, the probability of being in each class, given that a child has lead poisoning, and the probability of sequelae for each class of lead toxicity, given that the child is treated or not treated.

TABLE 1. True-Positive Rate and False-Positive Rate for Various Protoporphyrin Decision Thresholds (Second National Health and Nutrition Examination Survey Data)*

EP DT, μg/dL	Children With Lead Poisoning (n = 313)			Children Without Lead Poisoning (n = 2360)			Slope of the Tangent to the ROC Curve
	n	TPR	1 SD	n	FPR	1 SD	
10	313	1.00	0.00	2360	1.00	0.00	0.0
15	282	0.90	0.02	2114	0.90	0.01	0.7
20	197	0.63	0.02	1345	0.57	0.01	0.7
25	147	0.47	0.03	475	0.20	0.01	1.1
35	73	0.23	0.02	96	0.04	0.00	2.1
50	33	0.11	0.02	23	0.01	0.00	3.8

* Lead poisoning defined as a blood lead level ≥25 μg/dL. The slope of the tangent to the receiver operator characteristic (ROC) curve was determined by drawing a line tangent to the receiver operator characteristic curve at the decision threshold and measuring the rise over the run. EP DT, erythrocyte protoporphyrin decision threshold; TPR, true-positive rate; FPR, false-positive rate.

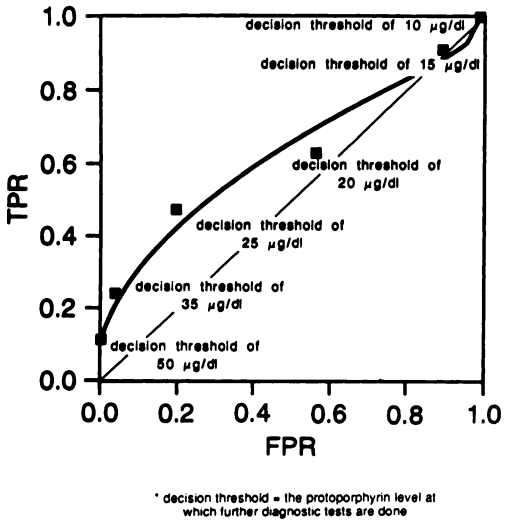

Fig 1. The receiver operator characteristic curve for the national population of children ≤6 years of age. True-positive rate (TPR) is defined as the number of children with a blood lead level ≥25 μg/dL and erythrocyte protoporphyrin level greater than or equal to the decision threshold divided by the number of children with blood lead level ≥25 μg/dL. False-positive rate (FPR) is defined as the number of children with a blood lead level <25 μg/dL and erythrocyte protoporphyrin level greater than or equal to the decision threshold divided by the number of children with a blood lead level <25 μg/dL. Figure 1 is based on the second National Health and Nutrition Examination Survey (NHANES II) data shown in Table 1. Each point denotes a different decision threshold.

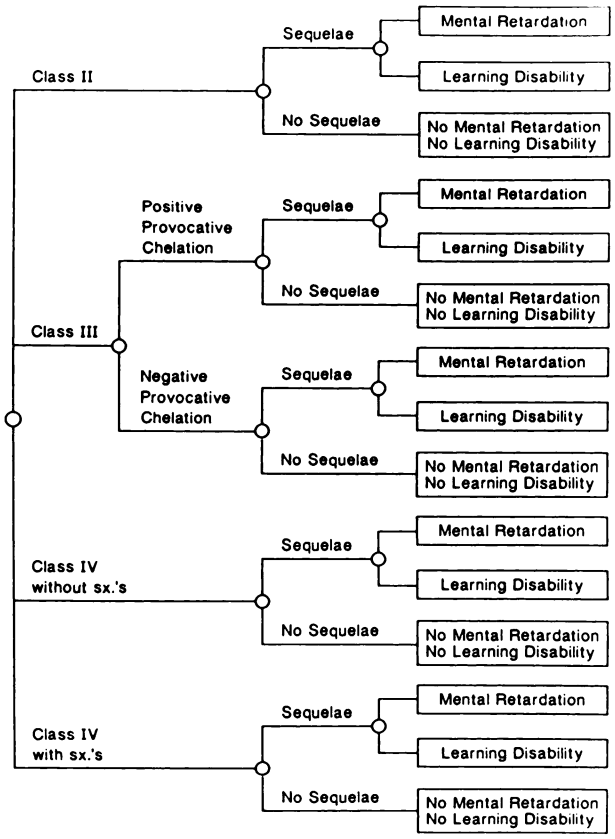

Fig 2. Tree representation of the events that follow a true-positive result of screening for lead poisoning.

Direct Medical Cost of Lead Poisoning

We based our calculation of the direct medical cost of the four outcomes of testing on the average medical care that a child would experience if a pediatrician were to follow the recommendations of the CDC. We assumed that lead screening was done as part of a well-child examination and that the direct medical costs that were incurred would be typical for a pediatrician in general practice in 1986.

Direct Medical Care Cost of a True-Positive Result. The average direct medical care cost of treating a child correctly identified as having lead poisoning was $1463. The cost is the sum of the costs of treating a child in each toxicity class weighted by the proportion of children in the class (Table 3).

Each child with correctly diagnosed lead poisoning was assumed to have an initial office visit with laboratory fees ($63) and a follow-up visit with laboratory fees ($105). Because of the wide range

TABLE 2. Probabilities of Events Associated With Lead Poisoning*

Event	Probability Estimate
True-positive screening result	
Class II	0.863
Sequelae	0.135
Learning disabilities	0.930
Mental retardation	0.070
No sequelae	0.865
Class III (provocative chelation done)	0.109
Positive results	0.400
Sequelae	0.225
Learning disabilities	0.890
Mental retardation	0.111
No sequelae	0.775
Negative results†	0.600
Sequelae	0.180
Learning disabilities	0.910
Mental retardation	0.090
No sequelae	0.820
Class IV without symptoms of lead poisoning	0.023
Sequelae	0.225
Learning disabilities	0.880
Mental retardation	0.120
No sequelae	0.875
Class IV with symptoms of lead poisoning	0.005
Sequelae	0.500
Learning disabilities	0.550
Mental retardation	0.450
No sequelae	0.500
False-negative screening result	
Class II	0.863
Sequelae	0.270
Learning disabilities	0.930
Mental retardation	0.070
No sequelae	0.730
Class III	0.109
Sequelae	0.450
Learning disabilities	0.890
Mental retardation	0.110
No sequelae	0.550
Class IV without symptoms of lead poisoning‡	0.023
Sequelae	0.450
Learning disabilities	0.880
Mental retardation	0.120
No sequelae	0.550
Class IV with symptoms of lead poisoning	0.005
Sequelae	1.000
Learning disabilities	0.530
Mental retardation	0.470
No sequelae	0.000

* The percentage of lead-poisoned children in each class was obtained from the second National Health and Nutrition Examination Survey (NHANES II). Except for provocative chelation therapy, the probability of developing sequelae from lead poisoning was obtained from Berwick and Komaroff's analysis.[16]

† The percentage of children who have a negative provocative test and subsequently develop sequelae is unknown. The probability of developing sequelae after a negative provocative test was estimated by taking the average of the probability of sequelae in class II and class III with a positive provocative test.

‡ The percentage of children who were class IV was determined from NHANES II; however, there was no assessment of whether symptoms were present. We estimated that approximately 20% of the children in class IV had symptoms.

TABLE 3. Total and Weighted Direct Medical Care Costs of Each Class of Lead Poisoning

Class	Actual Cost, $	Weighted Cost, $*
Class II	1 200	1 036
Class III with positive provocative treatment	3 723	162
Class III with negative provocative treatment	1 946	127
Class IV with no symptoms	3 569	82
Class IV with symptoms	10 891	55
Total		1 463

* Weighted direct medical cost equals the actual cost multiplied by the proportion of lead-poisoned children in the class.

of possible charges associated with a child with lead poisoning, a base case was assumed. The following assumptions were made about the base case: (1) the child with a diagnosis of lead toxicity was 3 years old; (2) the child was monitored for lead poisoning until he or she reached the age of 6; and the total charges for the office visits that occurred 1, 2, and 3 years after diagnosis were discounted at a rate of 6% annually; (3) the child with diagnosed and treated lead poisoning did not have subsequent episodes of lead poisoning.

The CDC recommends specific treatment and medical follow-up protocols for each toxicity class.[2] We used the charges associated with these protocols to approximate the costs that would be incurred by a child in each disease class. Except for one charge, we used the fee schedule for the outpatient and inpatient pediatric department of Santa Clara Valley Medical Center, Santa Clara County, California, for 1986. The exception was the determination of an EP level. We used the charge for the EP measurement by the public health department for the state of New York ($5) to approximate the cost in states where lead poisoning screening is done routinely as part of the well-child visit. We used Santa Clara Valley Medical Center and New York State charges because they were readily available.

The estimated cost for a medical follow-up visit after treatment was $71. The CDC's protocol for each follow-up visit requires a hematocrit, EP, and/or lead determination, depending on the time of the visit and the disease class. A base laboratory fee for each visit was taken as the averaged charge of (1) a hematocrit plus an EP level; and (2) a hematocrit, EP, and blood lead level.

An essential part of the evaluation of a child with lead poisoning is the assessment of the home environment for lead exposure. The cost of a public health nurse home visit for 2 hours in Santa Clara County was estimated as $28.00, which is derived from the average hourly wage of a public health nurse who has home visits as part of her job description.

Direct Medical Care Cost of a True-Negative Result. The direct medical cost of a true-negative ($63) was the sum of the costs of a yearly well-child office visit ($30), a complete blood cell count ($28), and EP determination ($5).

Direct Medical Care Cost of a False-Positive Result. A false-positive result is, by definition, a positive EP followed by an evaluation that shows a blood lead level <25 μg/dL. The direct medical care cost of a false-positive ($105) was the sum of the costs of an office visit ($30), complete blood cell count ($28), EP determination ($5), blood lead determination ($16), and serum iron with total iron binding capacity ($26).

Direct Medical Care Cost of a False-Negative Result. The direct medical care cost of a false-negative was the cost of the initial office visit ($63). Lead poisoning might subsequently be correctly diagnosed in a child with a false-negative result, and the child would be treated; however, we did not model any medical treatment and follow-up costs that might be incurred in the future.

Indirect Cost of Lead Poisoning

The human capital approach was used to determine the indirect cost of lead poisoning.[17] In this approach, an illness that causes a reduction in future earnings is considered to have an indirect cost to society. The major forms of morbidity from lead poisoning are mental retardation and learning disabilities. Children who are mentally retarded as a result of lead poisoning were assumed to have an average intelligence quotient (IQ) between 50 and 70, the level that previous cost-benefit studies of lead poisoning assumed.[16,18] Conley[19] states that one of the better studies on the earnings of mentally retarded persons showed that the annual earnings were reduced by 14% compared with a person of normal intelligence, and we assumed this value for our analysis.

The average future earnings, discounted at 6% per year, of a 3-year-old male and female child in 1980 were $222 067 and $183 597, respectively.[20] We

estimated the average future earnings for a child in 1985 by using the average weekly earnings in 1980 and 1985 to create an earning index of 1.33.[21] The resulting average future earnings of a male and female child are $295 349 and $244 184, respectively. In our analysis we used future earnings of a generic child, $269 767, which is the average of the future earnings of a 3-year-old male and female. A 14% reduction in annual earnings results in a lifetime loss of $37 673.

The other effect of lead poisoning that leads directly to loss of income is learning disability without mental retardation. The loss of annual income attributable to learning disability has not been estimated in prior published studies. Our analysis was done with a reduced annual income of 7% for a child with a learning disability. The earnings loss was discounted at a rate of 6% each year.

Indirect Cost of a True-Positive Result. The indirect cost of a true-positive result was $2898. Indirect costs for a true-positive occur when a child is screened, detected as having lead toxicity, treated, but develops either mental retardation or learning disability. To calculate the average indirect cost of a true-positive, we used a tree representation to structure the sequence of events. Each event has an associated probability of occurrence and an indirect cost. The expected cost of each event is the probability of the event multiplied by its indirect cost. Figure 2 represents a true-positive outcome, a child with lead poisoning who was treated.

Indirect Cost of a False-Negative Result. The indirect cost of a false-negative result was $6096. Indirect costs of a false-negative result occur when a child with lead toxicity is not detected by the screening test and develops mental retardation or learning disability. We estimated these costs by the same method as the indirect costs of a true-positive result.

Indirect Cost of True-Negative and False-Positive Results. There are no indirect costs associated with a true-negative or a false-positive outcome because these results occur, by definition, in children who do not have lead poisoning.

Selecting the Optimal Threshold Value for Erythrocyte Protoporphyrin

The optimal EP decision threshold, the definition of an abnormal result that maximizes the utility of screening for lead poisoning, was determined with the following assumptions: disease prevalence of 12%, a 6% discount rate of future earnings, a 14% and 7% annual reduction in annual earnings secondary to mental retardation and learning disability, respectively.

The optimal EP decision threshold for each set of assumptions was calculated in the following manner: (1) we drew a line tangent to the ROC curve at each decision threshold (10, 15, 20, 25, 35, and 50 μg/dL); (2) we measured the slope of each tangent line (Table 1); (3) we used equation 1 to calculate the slope of the ROC curve at the optimal decision threshold, given our baseline set of assumptions about the costs of screening and the prevalence of lead poisoning; (4) we compared the calculated slope (step 3) to the measured slope of the ROC curve at each decision threshold (step 2); (5) when we found that the calculated slope of the tangent line at the optimal EP decision threshold was intermediate between the measured slopes for two decision thresholds on the ROC curve (step 2), we extrapolated between the two decision thresholds to set the optimal decision threshold; (6) the measured slope was never less than 0.6, as shown in Fig 1. For some sets of assumptions about cost and prevalence the calculated slope of the tangent to the ROC curve was less than 0.6. When the calculated slope of the tangent to the ROC curve was less than 0.6 there was no calculable optimal EP decision threshold.

RESULTS

The ROC curve was generated from the NHANES II data set on 2673 children 6 years of age or younger who had both a blood lead and an EP determination. The range of true-positive rate obtained from the ROC curve was 0.11 to 1.0. A true-positive rate of 0.11 corresponds to a decision threshold of 50 μg/dL, a level that has previously been described as unacceptably high.[2,8] A true-positive rate of 1.0 corresponds to an EP decision threshold of 10 μg/dL, a level that is well within the range in normal children. The range of false-positive results was 0.01 to 1.0, corresponding to a EP decision threshold of 50 μg/dL and 10 μg/dL, respectively. Based on the ROC curve in this analysis, the currently accepted decision threshold of 35 μg/dL has a true-positive rate of 0.23 and a false-positive rate of 0.04.

With the currently recommended decision threshold, erythrocyte protoporphyrin discriminates poorly between children whose blood lead is lower than 25 μg/dL and children whose blood lead is above this level. In fact, for a lead poisoning prevalence of 12%, the predictive value of a positive screening test (the probability that a positive screening result (an EP level of ≥ 35 μg/mL) will have a blood lead level ≥25 μg/dL) is 0.4. The probability that a negative screening result (an EP level of < 35 μg/mL) will have a blood lead level

≥25 μg/dL is 0.10, which is not very different from the pretest probability of lead poisoning, 12%.

We used equation 1 (see Appendix) to identify the point on the ROC curve that corresponds to the EP decision threshold that maximizes the expected benefits of screening. Equation 1 requires the costs of a true-positive result ($4361), a true-negative result ($63), a false-positive result ($168), and a false-negative result ($6159) and the nationwide prevalence of lead poisoning (12%). The calculated slope of the tangent to the ROC curve at the optimal EP decision threshold is 0.4. The lowest measurable slope of a tangent to the ROC curve in Fig 1 is 0.6, which corresponds to a EP decision threshold less than 25 μg/dL. Therefore, there is no EP decision threshold that maximizes the benefits of screening.

Sensitivity Analysis

To do our analysis, we made several assumptions about direct and indirect costs and prevalence of lead poisoning. To determine the effect that each assumption had on the result, we did a sensitivity analysis for each of these variables.

Effect of Prevalence of Lead Poisoning. At a prevalence of lead poisoning of 1%, the optimal EP decision threshold is indeterminate because the calculated tangent to the slope, 5.30, is greater than the maximum tangent to the slope on the ROC curve, 3.8. As the prevalence of lead poisoning increases from 1% to 3% and the assumptions remain the same, the optimal decision threshold is 35 μg/dL, the CDC's currently recommended EP decision threshold. As the prevalence increases to 8%, the optimal EP decision threshold decreases to approximately 25 μg/dL. For a disease prevalence greater than 8%, the optimal tangent to the slope will be less than 0.6, which does not correspond to any point on the ROC curve. As a result, there is no EP decision threshold that maximizes the benefit of screening when the prevalence of lead poisoning is greater than 8%.

Effect of Discount Rate of Future Earnings. At an annual discount rate of 4%, there was no effect on the optimal EP decision threshold for the base assumptions. At a 10% discount rate, under the same assumptions, the direct medical care cost was greater than the earnings lost from lead poisoning, indicating that the cost of screening would be greater than the expected benefits gained from screening.

Effect of Earnings Loss Secondary to Mental Retardation and Learning Disability. When either the reduction in earnings attributable to mental retardation or learning disability is increased from 14% and 7%, respectively, the slope of the tangent to the ROC curve at the optimal operation point is less than 0.6. Thus, under the base assumptions, when the loss of income secondary to mental retardation or learning disability is increased there is no optimal EP decision threshold that maximizes the benefits gained from screening. When the reduction in earnings attributable to mental retardation is reduced to 7%, the slope of the tangent to ROC curve at the optimal operation point remains less than 0.6.

Effect of Lead Screening Programs. When the effectiveness of preventing neuropsychological sequelae in children identified and treated for lead poisoning increases from 50% to 75%, the slope of the tangent of the ROC curve at the optimal operation point remained less than 0.6 and the decision threshold was indeterminate. Consequently an improvement in the estimated effectiveness of lead screening programs does not change the results of our analysis. On the other hand, when the effectiveness of the lead screening program is reduced to 25%, the slope of the tangent of the ROC curve at the optimal operation point corresponds to a EP decision threshold of 25 μg/dL.

DISCUSSION

As more has been learned about the toxic effects of lead, the CDC has lowered the definition of an elevated blood lead level to be sure that treatment is given to all who might benefit. The current definition of an elevated blood lead level, ≥25 μg/dL, is almost one half of the previous definition (≥40 μg/dL). However, since the definition of lead poisoning has been changed, the utility of EP as a screening test for lead poisoning has not been assessed critically. Using the current definition of an elevated blood lead level, we studied the utility of screening for lead with EP.

Our study has an empirical and theoretical component. The empirical component is an ROC curve, derived from a study of children, of a specific screening test for lead poisoning, EP. The theoretical component is a calculation that can be used to identify the decision threshold that maximizes the utility of screening for lead poisoning. We hoped to link these two components by using the theoretical calculation and the empirical ROC curve to identify the optimal decision threshold for EP screening. We were unable to achieve this goal, because the poor test performance of EP, as indicated by the ROC curve, did not allow us to identify an optimal EP decision threshold. Nevertheless, the two components of the study are useful in themselves. The empirical component demonstrates that EP is a poor screening test for lead poisoning and that

alternative strategies should be considered. The theoretical component can be used to assess future screening tests for lead poisoning, inasmuch as the calculation depends only on the cost and benefits of the four results of screening and the prevalence of the disease.

The poor performance of the EP screening test is not surprising. Using NHANES II as the study population, Mahaffey[14] demonstrated that an EP decision threshold of 30 μg/dL was able to identify only 53% of the children with a blood lead level ≥30 μg/dL. Furthermore, Piomelli et al[7] indicated that there is no correlation between a blood lead level ≤40 μg/dL and the EP level.

The Environmental Protection Agency and the Agency for Toxic Substances and Diseases Registry have recently stated that neurotoxicity is found at blood lead levels as low as 10 to 15 μg/dL.[22,23] Hence the blood lead level that represents lead poisoning may again be redefined. Rather than resetting the EP screening decision threshold to account for the change in the definition of lead poisoning, utility of the EP screening test should be reassessed.

There are several shortcomings to our study as discussed below.

Assessment of the Indirect Cost of Lead Poisoning

We used the human capital approach to assess the indirect cost of mental retardation and learning disability. With the human capital method, the value of an individual's life is measured as his or her discounted future earnings potential.[17] The overall effect of using the human capital approach is to underestimate the indirect cost of lead poisoning to society. Our model allows only for effects of lead poisoning that have a direct impact on future earnings, such as mental retardation and learning disability. This analysis does not account for other effects of lead poisoning that may not alter a person's earning potential but may affect the quality of life (ie, pain from colic).

An important characteristic of the human capital approach is sensitivity to the discount rate for future earnings. We used a 6% annual discount rate. If we had used a 10% rate, the cost of a true-positive test result would have been greater than the cost of a false-negative test result because the direct cost of treating lead poisoning would have been greater than the earnings loss from a child with lead poisoning.

Detection of Other Disease

In this model, a false-positive test result was considered as a cost, even though an abnormal EP level in a child without lead poisoning may signify asymptomatic iron deficiency (elevated EP levels can be an indication of iron deficiency that was undetected by a hemogram). To date, there has been no study of the long-term benefit of early detection of iron deficiency and we had no basis for including it as a benefit of screening.

Probability of Mental Retardation and Learning Disability From Lead Poisoning

In this analysis the probability of becoming mentally retarded or learning disabled was estimated using Berwick and Komaroff 's study.[16] At the time of their analysis, the CDC's classification of lead poisoning was slightly different from their current categorization scheme. The current class II is defined by a lower blood lead level (≥25 μg/dL) than the CDC used when Berwick and Komaroff estimated the probability of learning disability due to lead poisoning. There is no reason to believe that this change will substantially alter the predicted probability of sequelae from lead poisoning, inasmuch as there have been no data to define what lower threshold of a blood lead level will result in neuropsychological sequelae.

Additionally, we have estimated two probabilities that were not reported in Berwick and Komaroff 's study: (1) the percentage of children who have a positive or negative lead provocative test and subsequently developed sequelae; and (2) the percentage of children who are class IV with and without symptoms. When these two variables were set at estimated extreme upper and lower limits, the results were unchanged, because these variables make a small contribution to the total cost of treating a child with lead poisoning.

Cost of Mental Retardation and Learning Disability

The expected annual reduction of earnings secondary to mental retardation, 14%, is a conservative estimate derived from a study that was done in 1960.[19] This study compared the earnings of mentally retarded persons with those of normal persons. In 1986, the reduction in earnings secondary to mental retardation should be higher than in 1960, because labor-intensive jobs have decreased since 1960 and highly technical jobs have increased. One would expect that a mentally retarded person who could perform a labor-intensive job would be less able to do a highly technological job. Furthermore, the model assumes that the employment rate of mentally retarded individuals is the same as that of normal individuals.

In summary, our estimate of the loss of earnings associated with mental retardation and learning disability is lower than what actually may be. However, as indicated in the sensitivity analysis, increasing the loss of earnings attributable to mental retardation or learning disability will not alter the results of the study.

Total Societal Cost of Lead Poisoning

We assessed the societal cost of lead poisoning as the direct medical care cost of a child with lead poisoning and the loss of income attributable to lead poisoning. The model excluded costs that would not be considered uniform for all lead-poisoned children. For example, the cost of residential abatement of lead paint was not included nor the cost of a parent's time to bring the child to and from the office. The addition of both of these costs would increase the cost of treating a child with lead poisoning. The cost of other intangibles related to untreated lead poisoning, such as pain, inconvenience, and time out of school because of illness, were not addressed. Adding these costs would raise the total cost of a false-negative screening result.

Effectiveness of Lead Screening Programs

There has been no published study on the effect that lead screening programs have in reducing mental retardation and learning disability in children who have been identified as having lead poisoning. We made a conservative estimate that lead poisoning programs are 50% effective in preventing the sequelae of lead poisoning once it has been identified and appropriately treated. More effective lead screening programs would not have changed the results of our analysis.

Effect of Subsequent Screening at a Later Age

Our model did not take into account the possibility that a child with a false-negative EP result would be rescreened the following year and identified as having lead poisoning. In addition, we did not model the care of a child who was correctly identified as not having lead poisoning in one year but developed lead poisoning the following year. Both situations would have required more complex decision models than were used.

CONCLUSION

The measurement of blood lead concentration has not customarily been viewed as a screening test because it is both expensive and difficult to perform accurately. As a result, EP measurement has been used as an inexpensive alternative for lead screening. We addressed the following issue: Is EP an adequate screening test for lead toxicity as currently defined by the CDC? If so, what is the best decision threshold? Currently, the recommended EP decision threshold is 35 μg/dL.

We used a national population-based sample to construct a ROC curve to assess the relationship between the true-positive rate and false-positive rate of EP at various decision thresholds for screening of lead poisoning. The ROC curve showed that EP simply does not discriminate well enough between children with and without an elevated blood lead level. Additionally, we used the ROC curve and decision analysis to determine the decision threshold that maximized the utility of EP screening for lead poisoning. Our findings indicate that at the present EP decision threshold of 35 μg/dL, too many children with lead poisoning are being missed and placed at risk of developing neuropsychological sequelae.

Our results strongly suggest that EP should not be recommended uniformly as a national screening test for lead poisoning. In communities where the prevalence of lead poisoning is low, such as 3%, the current EP threshold of 35 μg/dL may be appropriate. In areas in which the prevalence of lead poisoning is greater than 8%, EP measurement is not sensitive enough to identify individuals with lead toxicity.

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APPENDIX

Equation 1[9,10]

ROC curve slope at best operating point

$$= \frac{P(D-)}{P(D+)} \times \frac{CFP - CTN}{CFN - CTP}$$

where P(D+) = national prevalence of lead poisoning in children, P(D−) = 1 − national prevalence of lead poisoning, both in children ≤6 years of age, CFP = the cost of a false-positive result, CTN = the cost of a true-negative result, CFN = the cost of a false-negative result, CTP = the cost of a true-positive result, [CFP − CTN] = the cost of using the test in children without lead poisoning, and [CFN − CTP] = the benefit of using the test in children with lead poisoning.

REFERENCES

1. American Academy of Pediatrics. Acute and chronic lead poisoning. *Pediatrics* 1971;47:950–951
2. Centers for Disease Control. *Preventing Lead Poisoning in Young Children: A Statement by the Centers for Disease Control.* Atlanta, GA: US Dept of Health and Human Services; January 1985
3. Piomelli S, Seaman C, Zullow D, Curran A, Davidow B. Threshold to lead damage to heme synthesis in urban children. *Proc Natl Acad Sci USA.* 1982;79:3335–3339
4. Mahaffey KR, Rosen JF, Chesney RW, Peeler JT, Smith CM, DeLuca HF. Association between age, blood lead concentration, and 1,25-dihydroxycholecaliferol levels in children. *Am J Clin Nutr.* 1982;35:1327–1331
5. Angle CR, McIntire MS. Low lead level and inhibition of erythrocyte pyrimidine nucleotidase. *Environ Res.* 1978; 17:296–302
6. Needleman HL, Gunnoe C, Leviton A, Linn S, Schoenbaum S. Deficits in psychological and classroom performance of children with elevated dentine lead levels. *N Engl J Med.* 1979;300:689–695
7. Piomelli S, Davidow B, Guinee V, Young P, Giselle G. The FEP (free erythrocyte porphyrin) test: a screening micromethod for lead poisoning. *Pediatrics.* 1973;51:254–259
8. American Academy of Pediatrics. Statement on childhood lead poisoning. *Pediatrics.* 1987;79:457–465
9. Metz CE. Basic principles of ROC analysis. *Semin Nucl Med.* 1978;8:283–298
10. McNeil BJ, Keeler E, Adelstein SJ. Primer on certain elements of medical decision making. *N Engl J Med.* 1975;293:211–215
11. McDowell A, Engel A, Massey JT, Maurer K. *Plans and Operation of the Second National Health and Nutrition Examination Survey, 1976–1980.* Washington, DC: Public Health Service, US Government Printing Office; 1981. Vital and Health Statistics Series 1, No 15, kDHHS, Public Health Service publication 81-1317
12. Graef JW. *Lead Absorption in Children.* Chisolm JJ, O'Hara DM, eds. Baltimore, MD: Urban & Schwarzenberg; 1982:153–164
13. Centers for Disease Control. *Laboratory Procedures Used by the Clinical Chemistry Division, Centers for Disease Control, for the Second National Health and Nutrition Examination Survey (NHANES II) 1976–1980.* Atlanta, GA: Centers for Disease Control; 1981
14. National Center for Health Statistics. *Blood Lead Levels for Persons 6 Month–74 Years of Age: United States, 1976–1980.* Hyattsville, MD: Public Health Service; 1982. Advance Data From Vital and Health Statistics. No 79. US Dept of Health and Human Services publication (PHS)82-1250
15. Mahaffey KR, Annest JL. Association of erythrocyte protoporphyrin with blood lead level and iron status in the second National Health and Nutrition Examination Survey, 1976–1980. *Environ Res.* 1986;41:327–338
16. Berwick DM, Komaroff AL. Cost effectiveness of lead screening. *N Engl J Med.* 1982;306:1392–1398
17. Rice DP. *Estimating the Cost of Illness.* Washington, DC: US Government Printing Office; 1966. Health Economics Series No 6. Public Health Service publication 947-946
18. Provenzano G. Low level lead exposure. In: Needleman HL, ed. *Low Level Lead Exposure.* New York, NY: Raven Press; 1980:299–315
19. Conley RW. *The Economics of Mental Retardation.* Baltimore, MD: Johns Hopkins; 1973:161–240
20. Rice DP, Hodgson TA, Kopstein AN. The economic cost of illness: a replication and update. *Health Care Financing Rev.* Fall 1985;7:67–80
21. US Dept of Labor and Statistics. *Employment and Wages 1985.* Bureau of Labor and Statistics Bulletin 22776, November 1986
22. *Air Quality for Lead.* Research Triangle Park, NC: Environmental Protection Agency; 1986. Publication EPA/660/8-83/028af
23. Agency for Toxic Substances and Diseases Registry. *The Nature and Extent of Lead Poisoning in Children in the United States: A report to Congress.* Atlanta, GA: Dept of Health and Human Services; 1988

SOWING THE SEEDS OF A VIOLENT FUTURE

In general, the families that suffer the most social stress receive the least social support. The widening gap in this country between rich and poor make it even more likely that these [needy] children will repeat their parents' poverty. They will not be prepared to contribute to society - except in an antagonistic, often violent way.

Brazelton TB. Why is America failing its children. *The New York Times Magazine.* September 9, 1990.

SUBMITTED BY STUDENT