

Nutritional and socio-economic status in the prognosis of childhood acute lymphoblastic leukemia

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The survival of children with acute lymphoblastic leukemia (ALL) living in developing countries is lower than that of children in developed countries. Few studies have specifically investigated the influence of nutrition and socio-economic factors on the prognosis of children with ALL. Ethnic origin may be a confounding factor in many reports. A systematic review was undertaken comprising primarily all articles which contained medical subject headings of the Index Medicus related to nutrition disorders and socio-economic factors in children with ALL from 1970 through 2000. Special emphasis was given to our own experience. In a previous study we investigated the relative impact of malnutrition and socio-economic status on the outcome of ALL adjusting for the known influence of biological factors. The estimated 12-year probability of survival in continuous remission was 59% (SE 5%) for the group of well-nourished children with *good* socio-economic status and 27% (SE 7%) for the group of well-nourished children with *poor* socio-economic status ($p < 0.0002$). The same estimates for children with *poor* socio-economic status divided according to their state of nourishment was much less statistically significant (well-nourished, 27%, SE 7% vs. undernourished, 6%, SE 6%) ($p = 0.053$). Differences in the relative distribution of biological subtypes in children from diverse socio-economic strata are possible and were investigated. We did not find any difference in the distribution of monthly *per capita* income earned by families of children with the pre-B CD10 positive phenotype compared to those with the CD10 negative phenotype ($p = 0.32$). Likewise, no difference was detected between children with the T-phenotype compared to those with the pre-B CD10 positive phenotype ($p = 0.14$). We were also unable to demonstrate any difference in the distribution of monthly *per capita* income earned by families of children whose abnormal clones had more than 50 chromosomes compared to those with 50 chromosomes or less ($p = 0.68$). Non-compliance with treatment is a strong hypothesis to explain

the marked influence of nutritional and socio-economic factors on the prognosis of ALL in children. In our experience, a specific questionnaire indicated that 13 out of 34 children (38.2%) admitted that they had not taken oral medication at least once in an 8-week period. Assays of 6-mercaptopurine metabolites in red blood cells are under way. More data on children's compliance with treatment and its relation to the socio-economic and cultural background of their families will be necessary to understand the phenomenon and help children from low socio-economic strata to have a chance of cure similar to those more socially privileged.

The overall survival curves for children with acute lymphoblastic leukemia (ALL) living in underdeveloped or developing countries are clearly inferior to those derived from children in developed countries where the estimated probability of long-lasting remission (cure) now reaches 70% to 80%. Poorer treatment results in developing countries are probably due to several factors, such as biological heterogeneity of the disease, variability in drug metabolism,¹ concomitant infectious disease,² and inadequate health facilities, including lack of medications and supportive care, and advanced disease at diagnosis. Malnutrition and the socio-economic and cultural background of the family seem to be very important even in regions where facilities are substantially adequate. It is the purpose of this paper to review some studies which have attempted to determine the impact of the last two factors on disease-free survival. Before briefly describing the indicators which have been utilized for the characterization of malnutrition and socio-economic status, it is necessary to emphasize that ethnicity is a potential confounding factor in many studies which will be summarized. Black,³⁻⁹ Hispanic^{10,11} and Indian American children¹⁰ in the United States, Polynesian children in New Zealand,¹² Black children in South Africa,¹³ and Asian children in the United Kingdom¹⁴ are some examples of the interplay between socio-economic and ethnic factors. Nonetheless ethnicity may be an independent prognostic factor, via bio-

logical heterogeneity of leukemic cells, but this possibility has never been unequivocally demonstrated.

Anthropometric measures are the most widely used indicators of nutritional status. Standardized weight-for-age (WAZ), height-for-age (HAZ), and weight-for-height (WHZ) Z scores are easily recorded when an appropriate population data set for comparison is available.^{15,16} WHZ and WAZ are clearly insensitive for assessment of wasting conditions in children with large tumor masses. The use of mid-upper arm circumference, triceps skinfold thickness¹⁶ and body mass index (BMI: weight/height squared)¹⁷ results in greater sensitivity but these parameters also depend on a reference population. Biochemical tests, such as plasma proteins (pre-albumin, albumin, and retinol-binding proteins),¹⁶ may be useful adjuncts to measure wasting conditions more accurately. On the other hand, stunting chronic processes are adequately measured by HAZ score.¹⁵ Indicators of socio-economic status (SES) that have been used in the reviewed studies may be separated into two groups: a) the family unit is the basis for the classification (father's occupation,^{3,18,19} family income,²⁰ hospital pay code,¹¹ parental educational level²¹ or a combination of some indicators, such as *per capita* income, daily electric energy consumption, and house attributes;²² b) some area measure of social deprivation, based on which children are classified according to socio-economic characteristics of the area in which they live^{8,23} or are treated (private *versus* public hospital).⁷ One of the studies did not specify the criteria for socio-economic classification.²⁴

Reports dealing with nutritional data will be described first, then those with socio-economic data, and lastly studies which contain results derived from both. Appropriate mention will be made whenever ethnic considerations are the main focus of the study. The first data on nutritional status as a prognostic factor came from St. Jude Children's Research Hospital.⁴ No significant difference in clinical outcome was noted between groups of children with ALL when they were classified below the 25th, from the 25th to 75th, and above the 75th percentile regarding height-for-age or weight-for-age at diagnosis. Asian children living in the United Kingdom¹⁴ had a poorer prognosis than native white children. Although not specifically accounted for in the statistical analysis, the mean height-for-age Z scores were -0.26 and +0.2 for Asian and native white children, respectively. The corresponding WAZ scores were -0.53 and -0.16, respectively. In a recent paper²⁵ by the same author (Mann JR) the survival of Asians treated at Birmingham Children's Hospital was observed to be poorer than that of Whites in the period of 1980 to 1984, although for the entire period of 1975 to 1994 the outcome of both groups was similar. The authors recognize that poor treatment compliance might have contributed to that difference.

In their first publication Scottish researchers²⁶ reported that children in the lower third of the weight-for-height distribution had the highest risk of relapse ($p = 0.012$). In their second publication¹⁷ the same group was

not able to find any evidence that the body mass index standard deviation score was related to clinical outcome in 1,025 children with standard risk ALL treated with the MRC UKALL-X protocol. They concluded that the apparent effect of nutritional status in their earlier study was presumably due to the small sample size ($n = 78$) and an extreme of sampling variability. It is important to note that in both studies only acute wasting indicators of undernourishment (weight-for-height and body mass index) were considered. A group of investigators from Mexico²⁷ demonstrated that undernourishment may also affect the rate of early mortality caused by ALL. Children who weighed less than 80% of the weight expected for the height at diagnosis had 2.6 times (95% confidence interval 0.55–11.9) higher risk of dying during the induction phase of treatment than well-nourished patients. The risk of death tended to increase as the nutritional status progressed from normal to mild and severely abnormal ($p = 0.048$).

Although the main focus of a series of studies done at St. Jude Children's Research Hospital has been the prognostic influence of ethnicity,^{3,5,6} the pioneering study of 1972³ for the first time included socio-economic status as one of the possible explanations for differences in prognosis between Negro and Caucasian children with ALL. Differences in the median duration of hematologic remission and survival were very striking when Negro children were compared with Caucasian ones. Nevertheless also white children coming from the lowest socio-economic stratum had a poorer prognosis than those from higher strata. In their latest publication dealing with ethnicity,⁶ this group of researchers was not able to find any difference in outcome by race if only children in the most recent treatment era (since 1984 for ALL) were considered. They concluded that with equal access to effective contemporary treatment, black children with cancer fare as well as white children when treated with protocol-based therapy in a pediatric oncology research center. As the authors pointed out, these results are quite different from contemporary American national experience. A poorer 5-year survival rate for Negro compared with White children was identified for the years 1973 through 1987 and even a slight decrease in the survival rates for Negro children was shown for the period 1983 to 1987 compared with data from 1978 through 1982.²⁸

Another two studies dealing with striking differences in the prognosis of Black and Caucasian children recognized that socio-economic factors might be responsible for part of the observed difference in the results of treatment. The End Results Group in the United States⁷ reported that the one-year survival rate of 1,541 white children treated at private hospitals was better than that of 134 white children treated at county and charity hospitals. Similarly a study conducted in Baltimore,⁸ between 1960 and 1975 showed that the two-year survival rate for 23 white children coming from the low SES category was only 28% compared with 51% for 22 white children coming from the high SES category (p

< 0.005). In both studies the small sample size of Black children precluded valid analyses. Event-free survival and cure rate were lower for 82 Mexican-American as opposed to 90 European-American children treated at the M. D. Anderson Center in Houston (USA) between 1974 and 1985 and followed through 1994, but the differences were not statistically significant. Financial status of the patient's family as identified by hospital pay code was significantly lower for Mexican-American children ($p < 0.01$). Cure rate for the total patient group ($n = 172$) was clearly inferior for children with a lower pay code classification ($p = 0.01$), although all children were treated similarly, regardless of the financial status.¹¹

Based on the father's occupation at the time of the child's diagnosis of acute leukemia (75% lymphoblastic type), a study¹⁹ showed that 38% of the fathers of short-term survivors (less than two years after diagnosis) were in the semi-skilled, unskilled or farmer classification, as compared with 23% of the fathers of long-term survivors (at least five years after diagnosis). This difference, however, was not statistically significant.

Social class as a prognostic variable in acute lymphoblastic leukemia was the title of the first study dealing primarily with this factor.¹⁸ Australian children from upper social classes had a significantly better five-year survival rate and duration of first remission than children from lower social classes. The difference was even more striking when only children with a leukocyte count at diagnosis below $30 \times 10^9/L$ were considered.

Using the Carstairs index as an area measure of material deprivation, British investigators²³ were not able to find a statistically significant effect of socio-economic status on survival of children with ALL. It is noteworthy however, that when small differences were detected, children from the most deprived group were the most disadvantaged. It is also important to recall that the Carstairs index is a measure of economic deprivation within an enumeration district (area) and not of an individual family. It is conceivable that heterogeneity in the socio-economic status of children within an area may obscure an effect which would be detected if socio-economic status of individual families were recorded instead, as done by our group.

Similarly, Dutch investigators²¹ concluded that the influence of parental educational level, a putative indicator of socio-economic status, on the 10-year survival rate of children with acute lymphoblastic leukemia in The Netherlands appeared small or even equivocal. Small differences in socio-economic status and optimal geographic and financial access to care, delivered through national treatment protocols, might be responsible for the observed results. There are only two groups of researchers who have dealt with the simultaneous influence of nutritional and socio-economic status. Investigators from Puebla, Mexico,²⁹ unequivocally demonstrated, for the first time, that 16 undernourished children with ALL had a statistically significant lower chance of remaining in first complete remission than 27 well-nourished children (five-year event-free sur-

vival of 26% and 85%, respectively; $p < 0.001$). The main reason for the observed difference was the significantly higher rate of bone marrow relapse in the latter. The same group of investigators²⁰ reported that undernourishment was associated with low socio-economic status (r coefficient = +0.77) in such a way that children whose parents earned less than 1,000 dollars a month had an estimated probability of event-free survival of 45% at 70 months contrasting with 91% for children in the higher socio-economic stratum.

In our first study in Minas Gerais, Brazil,³⁰ we demonstrated that after adjustment for other well known prognostic factors in a Cox's model, children with a height-for-age Z score below -2 had a relapse rate 8.2 times greater (95% confidence interval 3.1 to 21.9) than children with a Z score above -2. In this study the nutritional indicator height-for-age Z score was a statistically more powerful prognostic factor than weight-for-age; weight-for-height was not significant at all. This was an indication that socio-economic factors probably played a more important role than nutritional status *per se* since it is well known that deficits in height-for-age reflect a chronic stunting process due to poor social conditions, whereas deficits in weight-for-height or body mass index denote a more acute wasting phenomenon. Weight-for-age represents the sum of the information given by the other two indices.¹⁵

In the second study²² we investigated the relative impact of malnutrition and socio-economic status on the outcome of an extended group of children with ALL adjusting for the known influence of biological factors. Socio-economic status was defined as the product of monthly *per capita* income (in minimal wages) times mean familial daily energy consumption (in kWh). The cut-off point for categorization between *poor* and *good condition* was 3.1. Socio-economic status and nutritional variables (height-for-age Z score) proved to be strongly associated ($p = 0.00001$). Figure 1 (updated as of March 31, 2000) depicts the simultaneous influence of these factors on continuous remission survival. The estimated twelve-year probability of survival in continuous remission was 59% (SE 5%) for the group of well-nourished children with a *good* socioeconomic status and 27% (SE 7%) for the group of well-nourished children with a *poor* socio-economic status ($p < 0.0002$). The same estimates for children with poor socioeconomic status, divided by their state of nourishment, was much less statistically significant (well-nourished, 27%, SE 7% vs. undernourished, 6%, SE 6%) ($p = 0.053$).

Table 1 summarizes all reviewed studies, listing the respective methods for measuring nutritional and socio-economic status indicators and the observed results.

Possible mechanisms underlying the impact of nutritional and socio-economic factors on outcome

In the reported Mexican study²⁹ shorter survival of undernourished children was secondary to bone marrow relapses. The basis for this relationship was attributed to

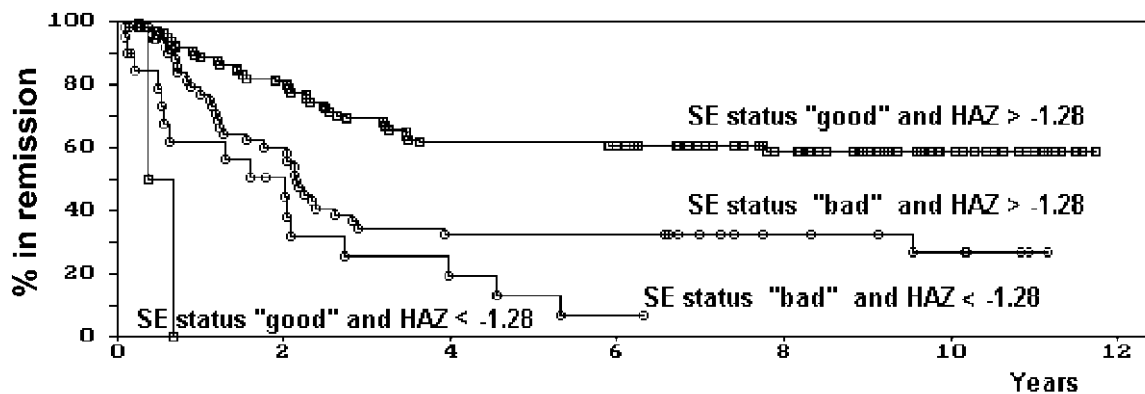


Figure 1. Kaplan-Meier plots for the duration of survival in continuous remission, comparing four groups of children according to height-for-age Z score ($>$ or $<$ -1.28) and socio-economic (SE) status. The estimated 12-year probability of continuous remission survival was 59% (SE 5%) for the group of well-nourished children with *good* socio-economic status and 27% (SE 7%) for the group of well-nourished children with *poor* socio-economic status (logrank test, $p < 0.0002$). The difference for the same estimates for children with *poor* socio-economic status was much less statistically significant (well-nourished, 27%, SE 7% vs. undernourished, 6%, SE 6%) ($p = 0.053$).

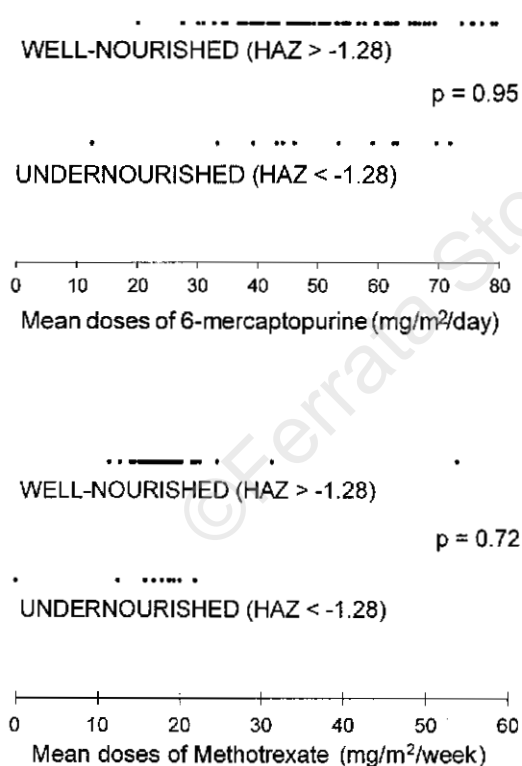


Figure 2. Mean daily doses of 6-mercaptopurine and weekly methotrexate prescribed for well-nourished and undernourished Brazilian children during the maintenance phase of treatment of acute lymphoblastic leukemia.^{30,31} Each point represents one child. HAZ means height-for-age Z score. Distributions are not significantly different (Mann-Whitney tests, $p = 0.95$ and $p = 0.72$, respectively, for 6-MP and methotrexate).

intolerance of myelosuppressive chemotherapy during the maintenance phase of the treatment, or to defective immunosurveillance of leukemic cells, increasing the relapse rate. The amount of maintenance drugs prescribed to those children was approximately half the optimal dose, which was very close to that received by well-nourished children ($p = 0.01$). We were not able to confirm this hypothesis. No difference in mean prescribed doses of 6-mercaptopurine or methotrexate was observed in well and undernourished children^{31,32} (Figure 2). The hypothesis of defective immunosurveillance has never been submitted to scientific investigation.

We rather favor the hypothesis that malnutrition is a confounding factor for the effect of socio-economic variables. By what mechanisms could poor socio-economic status affect outcome adversely?

Cost of drugs and availability of quality care are clearly the first to be mentioned. However these mechanisms were not really operative in the reviewed studies, in that the majority of investigators, including ourselves, explicitly stated that all children had free access to drugs and that treatment had been delivered by the same staff. Other possible mechanisms are the following:

(a) differences in the relative distribution of biological subtypes in children from diverse socio-economic strata. Preliminary unpublished data on the immunophenotypes of 144 children with ALL treated by our group from 1994 to 1998 indicate that there is no difference in the distribution of monthly *per capita* income earned by families of children with the pre-B CD10 positive phenotype compared with those with the CD10 negative phenotype ($p = 0.32$). Likewise, no difference was detected between children with the T-phenotype compared with those with the

pre-B CD10 positive phenotype ($p = 0.14$; Figure 3). We were also unable to demonstrate any difference in the distribution of monthly *per capita* income earned by families of children whose abnormal clones had more than 50 chromosomes compared to those with 50 chromosomes or fewer ($p = 0.68$, unpublished data, Figure 4);

(b) physicians' inability or failure to adhere to the doses recommended by the treatment protocol. In 76 Canadian children with standard risk ALL who were followed up for at least 5 years from diagnosis, 20 children received less than 60% of the recommended dose of methotrexate and 11 of them relapsed. Of the remaining 56 children who received more than 60% of the

Table 1. Summary of studies dealing with the impact of nutritional indicators (upper third), socio-economic status (middle third) or both (lower third) on outcome of children with ALL.

Study, ref. # (year)	Number of children	Measure of nutritional status, socioeconomic status, or both	Summary of Results
Simone ⁴ (1974)	358	Height and weight percentiles (<25; 25 to 75; >75)	No difference in survival or duration of complete or hematologic remission
Oakhill ¹⁴ (1983)	30 Asian; 60 White	Height-for-age and weight-for-age Z scores	Lower 5-year continuous complete remission for Asian children; effect of nutrition not reported
Reilly ²⁶ (1994)	70	Weight-for-height Z scores (<-0.5, -0.5 to +0.5; >0.5)	Significant poorer event-free survival for children with WHZ <-0.5 versus those >-0.5
Weir ¹⁷ (1998)	1,019	Body mass index Z score (<-0.5, -0.5 to +0.5; >0.5)	No influence on outcome
Mejia-Arangure ²⁷ (1999)	17 cases; 76 controls	Weight-for-height (malnutrition: <80% expected weight-for-height)	Higher risk of dying during induction for undernourished children
Walters ³ (1972)	46 Negro 288 White	Father's occupation	Poorer outcome for Negro and for children in lowest SE status group (Black and Caucasian)
Pendergrass ⁷ (1975)	126 Negro 1675 White	Hospital type (private vs county and charity)	One-year survival rate poorer for Black children. Among Whites, poorer for those treated in county and charity hospitals
Szkl ⁸ (1978)	27 Negro 184 White	Median rental values of census tracts for living area	Two-year survival rate poorer for Black children and for White children from low est SE status category (only in Baltimore; n = 23)
Hord ¹¹ (1996)	90 European/American 82 Mexican/American	Pay code at M.D. Anderson Hospital. All children received same treatment regardless of pay code	Event-free survival and cure rate lower for Mexican/American children (not significant). Full pay status (total group) associated with higher cure rate ($p = 0.01$)
Gibson ¹⁹ (1974)	59 long and 59 short survivors	Father's occupation	38% of short-term and 28% of long-term survivors belonged to low SE status category (statistically not significant)
McWhirter ¹⁸ (1983)	70	Father's occupation	5-year survival rate 57% for high SES and 26% for low SES
Coebergh ²¹ (1996)	508	Parental educational level (PEL)	5- and 10-year survival rates not significantly different for low and high PEL groups
Schillinger ²³ (1999)	5,556	Carstairs index (area measure of social deprivation)	5- and 10-year survival rates worse for the most deprived category (not significant)
Lobato-Mendizábal (1989 ²⁹ ; 1991 ²⁰)	43 (1 st study) and 49 (2 nd study)	Weight-for-age Z score; family income	5-year event free survival rate lower for undernourished children and low SE status groups
Viana (1994 ³⁰ ; 1998 ²²)	128 (1 st study) and 167 (2 nd study)	Z scores (weight-for-age, height-for-age, weight-for-height); family <i>per capita</i> income, daily electric energy consumption, house attributes	Children with HAZ < -2 had a relapse rate 8.2 times greater than those with HAZ > -2. See Figure 1 for simultaneous impact of nutritional and SE status.

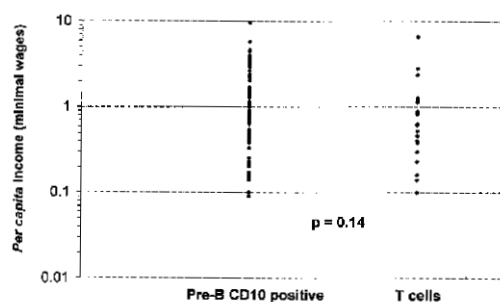


Figure 3. Distribution of the *per capita* income (minimal wages) in families of children with acute lymphoblastic leukemia, according to pre-B CD10 positive and T-immunophenotypes. Each point represents one child. The difference is not statistically significant (Mann-Whitney test, $p = 0.14$).

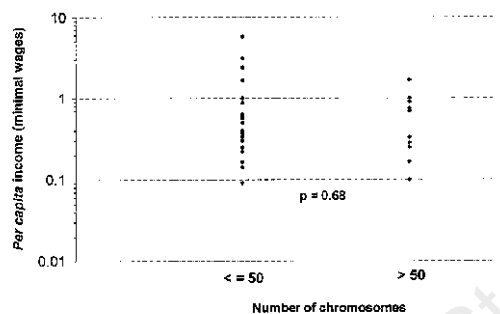


Figure 4. Distribution of the *per capita* income (minimal wages) in families of children with acute lymphoblastic leukemia, according to the number of chromosomes in the abnormal clone (< 50 or > 50). Each point represents one child. The difference is not statistically significant (Mann-Whitney test, $p = 0.68$).

scheduled methotrexate, only 16 relapsed ($p < 0.05$).³³ In our experience children who had never had their treatment drugs (oral daily 6-mercaptopurine and weekly methotrexate) discontinued during the maintenance phase had a significantly worse continuous survival curve than those for whom drugs had to be withheld for some time up to 10% of the total days of the maintenance phase because of bone marrow suppression.^{31,32} Those who had the drugs discontinued more than 10% of the maintenance phase had the worst prognosis (Figure 5). It is conceivable that physicians caring for children coming from low socio-economic strata may not increase the doses of maintenance drugs to the maximum tolerated, as recommended by the protocol, fearing complications;

(c) child's or family's non-compliance with treatment. The

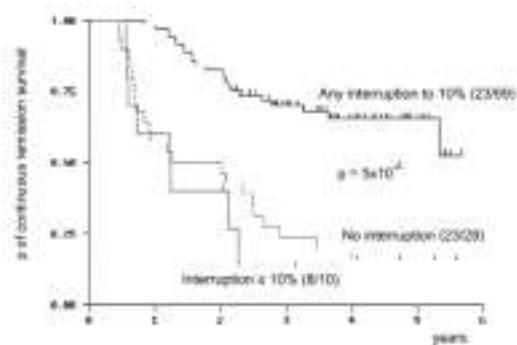


Figure 5. Kaplan-Meier plots for the duration of survival in continuous remission, comparing 3 groups of children according to the intensity of chemotherapy during the maintenance phase: no interruption of the drugs (middle line), interruption for up to 10% of the days of maintenance phase (upper line) and interruption for more than 10% of the days (lower line). The number of children with events out of the total in each group is indicated close to the corresponding curve. Vertical slashes indicate children who were censored in continuous complete remission. Differences between curves are highly significant (logrank test, $p = 5 \times 10^{-8}$).

plasma concentration of 6-mercaptopurine in 17 American children with ALL, who allegedly had received the drug two to four hours before blood collection, was not detectable in 9 out of 27 outpatient appointments. After taking the drug under medical supervision, all children had detectable plasma levels.³⁴ Morning urinary excretion of 6-mercaptopurine was assessed in 39 children who should have received the drug the previous evening.³⁵ In seven (18%), the drug was not detected. In another study, 496 British children had their blood collected for assays of 6-mercaptopurine metabolites in red blood cells:³⁶ 9 children (2%) were found to have completely undetectable metabolites on one or more occasions. A further 35 children had levels which were low enough to raise concern about the adequacy of the treatment. In our experience, preliminary results of a specific questionnaire indicate that 13 out of 34 children (38.2%) admitted that they had not taken oral medication at least once in an 8-week period. Almost half (6 children) had not taken the drugs 3 or more nights. Assays of 6-mercaptopurine metabolites in red blood cells are under way in this research and will probably demonstrate an increase in the frequency of non-compliant children. It will be necessary to prove, then, that non-compliance is more common in disadvantaged families, which is indeed a plausible hypothesis.

This review calls attention to the importance of including socio-economic factors in the reports of therapy for childhood ALL. Accordingly, these factors should be controlled for when comparisons of treatment are

made. The potential confounding role of children's ethnic origin and nutritional status should also be considered and adequately accounted for. Based on the results of our observation, we believe that non-compliance is a major mechanism underlying the noxious prognostic influence of low socio-economic status. Some practical measures for lessening the impact of it may be suggested: a) drug administration should be strictly monitored for all children and specially for those identified as being at greater risk of non-compliance. This would include, for instance, staff visits to the child's home; b) educational programs for the child and his or her family; c) pharmacologic controls such as assays of 6-mercaptopurine and methotrexate metabolite concentrations are not yet recommended because international experience with this method is not widely accepted as adequate and reliable; d) chemotherapeutic protocols specially devised for specific situations of high probability of non-compliance. Parenteral administration of maintenance phase drugs, if possible, is an interesting alternative, provided efficacy of the protocol is kept similar to standard treatment. As usual, carefully conducted clinical trials would have to be done before such protocols could be recommended for general use.

Although our results indicate that malnutrition is probably a confounding factor, provision of supplementary food for the child and the family should clearly be part of the total health care every child has the right to have. As stated in our previous paper,²² «*poor prognosis for leukemic children from low socio-economic strata is just another indicator of social inequality. Children do not vote, and they do not control wealth. They are dependent and are the most likely to suffer in conditions of poverty and to be pushed off the social safety net.*³⁷ *Health resources, and opportunities for education and information, should be available, more than ever, to the underprivileged in our societies.*

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