EVALUATION OF SURVIVAL IN MEDICALLY TREATED PATIENTS WITH HOMOZYGOUS BETA THALASSEMIA BY THE QUICK HIT METHOD

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Excellent: very good of its kind: eminently good: FIRST CLASS[1]
The least initial deviation from the truth is multiplied later a thousand fold.
Aristotle. *On the Heavens,* bk. I., ch. five[2]

ABSTRACT

Articles published in medical journals often evaluate the survival and/or prognosis of a medical impairment. The conclusions of these articles can be very misleading if correct mortality methodology is not utilized.

Authors evaluating survival in a cohort of individuals with Thalassemia Major concluded the prognosis was excellent. This was based solely on observed mortality. When the cohort is properly compared to the expected mortality of a similar nonimpaired population the result is quite different. Their survival is far from excellent. This article uses the quick hit method to evaluate the survival of this cohort having Thalassemia Major.

In the last issue of the *Journal of Insurance Medicine,* I presented a "quick hit method" to evaluate survival/mortality in clinical articles.[3] Recently, an article was published in the *New England Journal of Medicine* evaluating the prognosis of homozygous Beta Thalassemia (Thalassemia Major) in medically treated patients.[4] The authors conclude "the prognosis for survival without cardiac disease is *excellent* (my emphasis) for patients with thalassemia major who receive regular transfusions and whose ferritin concentrations remain below 2500 ng/ml with chelation therapy." Cardiac disease-free survival is defined as survival without the need for cardiac inotropic or antiarrhythmic medication.

The authors base their conclusion on only observed data. No comparison is made with expected survival data on a similar population. Characteristics of the study group at the end of follow-up:

59 patients alive, cardiac disease-free
18 patients alive, cardiac disease present
18 patients dead from cardiac disease
2 patients dead from unrelated causes

The overall cardiac disease-free survival for the entire cohort:

5 years	80 percent
10 years	65 percent
15 years	55 percent

Ferritin level was an excellent discriminator of cardiac disease-free survival. See Table 1. Of the three groups only the one with a ferritin level greater than 2500 ng/ml less than 33 percent of the time could be considered insurable risks. This group had a 15-year cardiac disease-free survival of 91 percent. The fate of the nine percent who developed cardiac disease is not stated. In the prechelation era, survival of individuals was only 50 percent after one year of onset of cardiac disease.[5] Therefore, many of the nine percent must be presumed to die in the ensuing few years. The use of chelation may well postpone but not eliminate death.

The authors note the end points in the study could have over estimated disease-free survival. Some of those not treated with cardiac medications may well have had cardiac disease if diagnostic testing had been undertaken.

The characteristics of the cardiac disease-free group are:

• Female/male	51 percent/ 49 percent
• Mean age at start of chelation therapy	10.5 ± 5.6 yrs.
• Follow up and entry period	1954 - 1975
• Duration of follow up	15 years

For simplicity, various assumptions and simplifications are made. The initial age interval will be 10-11. Since the male/female ratio

Table 1
Ferritin Level Greater Than 2500 ng/ml

	Less Than 33 Percent of Determinations Cardiac Disease-Free Survival	*34-66 Percent of Determinations Cardiac Disease-Free Survival*	*Greater Than 66 Percent of Determinations Cardiac Disease-Free Survival*
10 years	100%	48%	38%
15 years	91%	48%	18%

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was 49 percent/ 51 percent respectively, I used the United States 1980 Census Mortality table for the total population. In the calculations, other assumptions are: 1) the mean age of the group advances one full year for each yearly interval, and 2) the male/ female ratio remains constant over the 15-year duration.

Inspection of the survival curve of those cardiac disease-free raises worrisome long-term questions. Up to 10 years of continued chelation therapy, cardiac disease-free survival was 100 percent. Thereafter, the cardiac disease-free survival drops to about 97.5 percent at 12 years and 91 percent at 15 years. Nine percent developed cardiac disease over the final five years of follow-up. Of those, 6.5 percent developed cardiac disease in the final three years. This depicts a rapid acceleration in the development of cardiac disease. Whether this trend will continue is unknown.

The nine percent drop in cardiac disease-free included some alive with cardiac disease, some dead of cardiac disease. The authors noted of those not cardiac disease-free, 50 percent were alive with and 50 percent were dead of cardiac disease over the observation period. I will assume that this 50/50 split is also applicable to the nine percent not cardiac disease-free. Therefore, assume 4.5 percent died at the end of the 15-year follow-up period.

If chelation was begun at about age 10, most would be entering their late twenties or early thirties by the end of the 15-year follow-up period. Population mortality rates at these ages are stable succeeding the rapid teenage/ early twenties rise and preceding the inexorable age-related increase. The relationship of rising observed and stable expected deaths will lead to a marked rise in mortality ratios over the last five years of follow-up. What the curve will portray at 20 and 25 years is unknown. One must anticipate that the adverse survival trend beginning at 10 years of follow-up will continue. By virtue of the known high short-term mortality of those who develop cardiac disease and the relatively short follow-up of such a young group, the true long-term survival is unknown. I would strongly suspect it will never be better than at the end of the 15 years and in all probability will be worse. The strong possibility of underestimation of cardiac disease also needs to be kept in mind.

From the worksheet we see the expected mortality for an unselected population to be 1.39 percent for 15 years. This produces a mortality ratio (observed divided by expected) of about 325 percent. Were industry select tables used, the ratio would be higher.

Thus, whether we make a liberal (more than 4.5 percent die) or conservative (less than 4.5 percent die) assumption of death, mortality ratios are high and do not justify the conclusion of an excellent prognosis. Guarded prognosis is the appropriate conclusion.

WORKSHEET

- Age (at start of chelation therapy): 10
- Follow-up interval: 15 years
- Male 49 percent, female 51 percent
- Mortality table - life table for the total population, United States, 1979-1981
- Observed deaths at end of follow-up: 4.5 percent

Age	*Interval*	*Number Dying During Age Interval of 100,000 Born Alive*
10-11	0-1	19
11-12	1-2	19
12-13	2-3	24
13-14	3-4	37
14-15	4-5	52
15-16	5-6	67
16-17	6-7	82
17-18	7-8	94
18-19	8-9	102
19-20	9-10	110
20-21	10-11	118
21-22	11-12	124
22-23	12-13	129
23-24	13-14	130
24-25	14-15	130
25-26	15-16	128

Alive at beginning of age interval 10-11: 98,347
Dead at end of age interval 25-26: 1,365
Expected deaths through interval 0-16: 1.39 percent

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