



# Annotated Bibliography

## XII. Sickle Cell Disease and Thalassemia ii. Thalassemia



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### A. Clinical Aspects

(Also see [XV. New Concepts in Cord Blood Transplantation](#), [iii. Preimplantation genetic diagnosis](#))

#### 1. Quality of life and survival of patients with beta-thalassemia major. Cao A. Haematologica. 2004;89:1157-9.

In this concise editorial and commentary, the author points out that it is "gratifying" that, with modern supportive therapy, **"68% of patients with beta-thalassemia are alive at the age of 35."**

The most frequent causes of death are still heart failure and/or cardiac arrhythmia, which are mostly caused by myocardial iron overload. The second cause is intercurrent infections, and thrombotic events are emerging as an important complication and relatively frequent cause of death. Many patients still have cardiac disease and delayed pubertal development, and develop hypogonadism, hypothyroidism, hypoparathyroidism, and diabetes mellitus.

Data on the survival of patients and on quality of life are very useful in the genetic counseling of couples at risk of having beta-thalassemic offspring when planning a pregnancy, and in the discussion, with the parents of an affected child, on the available options for treatment of a newly diagnosed case. The pros and cons of traditional treatment should be evaluated vis-a-vis the results of bone marrow or cord blood stem cell transplantation. In this counseling, it should be pointed out that the only treatment that may lead to a definitive cure in thalassemia major is stem cell transplantation which, "even in the best conditions, is still associated with a mortality of 5% when performed from an HLA identical family donor."

*(Comment: The author indicates that, with modern supportive therapy, 32% of patients will die by the age of 35. The question that immediately comes to mind is, "If 100 children with beta-thalassemia major were to be transplanted at an early age, would 32 be dead at the age of 35?"*

*Transplants of young children using stem cell products from related or unrelated donors has a mortality much less than 32%. (See other citations in this segment of the Annotated Bibliography for further details of survival and disease free survival after transplantation for beta-thalassemia major -- emphasis should be on class 1 patients.) These data make a strong case for transplanting young children with beta-thalassemia major. When a matched-related or matched-unrelated adult donor cannot be found, matched unrelated umbilical cord blood should be used.)*

#### 2. Complications of ?-thalassemia major in North America. Cunningham MJ, Macklin EA, Neufeld EJ and Cohen AR for the Thalassemia Clinical Research Network. Blood 2004;104:34-39. [Abstract](#)

The authors indicate that the current clinical status of patients with thalassemia major remains poorly characterized. They performed a cross-sectional study of 342 transfusion-dependent patients in the Registry of the NIH-sponsored Thalassemia Clinical Research Network (TRCN). (Using TRCN criteria, ?-thalassemia major was defined as homozygous (or compound heterozygous) ?-thalassemia requiring 8 or more transfusions in the 12 months prior to enrolling in the Registry. Those with ?-thalassemia who required fewer transfusions are considered to have thalassemia intermedia and were not considered in the present report.)

The median patient age was 20 years. Thirty-five percent were seropositive for [hepatitis C virus \(HCV\)](#) or positive for HCV RNA (over the age of 24 years, 70% were positive). Among patients tested for both HCV antibody and RNA, 26 of 75 (35%) were subsequently HCV RNA negative. (Note: Transfusion-acquired HCV is presently an important problem among older patients with thalassemia, although improvements in viral screening of blood products have largely eliminated transfusion-transmitted HCV.)

Fifty-five percent of patients had undergone [splenectomy at a median age of 9 years](#). Twenty-three percent of the patients had a [hepatic iron content](#) >15 mg/g dry weight, a level at which more [aggressive chelation](#) has been recommended because of increased risk of morbidity and mortality. Twenty-three percent of patients 25 years or older had [heart disease requiring medication](#). (Cardiac failure and rhythm disturbances remain the main cause of death among young adults with thalassemia major.)

Of 232 patients who had liver biopsy, 10% had [cirrhosis](#). [Endocrinopathies](#) were quite common: of 130 patients 25 years or older 17% were receiving treatment for thyroid disease, 9% for parathyroid disease, 21% for diabetes, and 62% had received replacement therapy for hypogonadism. Among 328 patients who had received [chelation therapy](#) (deferoxamine - DFO) at some time, 32% reported complications requiring modification of the dose or route of administration of the chelator. Of 309 patients presently using DFO 20% reported current complications. Seventy four patients had [surgically placed central vascular access devices](#) (CVAD) within five years of Registry entry. Among 80 episodes of sepsis or [bacteremia](#), 90% were attributable to the CVAD; forty-three percent of patients with CVAD developed infections related to the device.

The authors point out that improved RBC transfusion schedules and iron chelation therapy have allowed children with thalassemia to avoid serious deformities and to have an improved life expectancy. However, compliance is a problem in a disease that requires lifelong treatment, and subcutaneous DFO delivered by pump is not an easy therapeutic program with which to comply.

*(Comment: The information provided in this article is valuable to physicians, patients and parents of affected children who*

must decide between transplantation and life long chelation therapy for transfusion-dependent thalassemia.)

3. **Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine.** Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, Romeo MA, Forni GL, Gamberini MR, Ghilardi R, Piga A, Cnaan A. *Haematologica*. 2004;89:1187-93. [Abstract](#)

Seven Italian centers reported data on survival, causes of death and appearance of complications in patients with thalassemia major. The interactions between gender, birth cohort, complications, and ferritin on survival and complications were analyzed. Survival after the first decade was studied for 977 patients born since 1960 whereas survival since birth and complication appearance was studied for the 720 patients born after 1970. Better survival was demonstrated for patients born in more recent years ( $p < 0.00005$ ) and for females ( $p = 0.0003$ ); **68% of the patients are alive at the age of 35 years**. In the entire population 67% of the deaths were due to heart disease. The prevalence of complications was: heart failure 6.8%, arrhythmia 5.7%, hypogonadism 54.7%, hypothyroidism 10.8%, diabetes 6.4%, HIV infection 1.7%, and thrombosis 1.1%. Lower ferritin levels were associated with a lower probability of heart failure (hazard ratio = 3.35,  $p < 0.005$ ) and with prolonged survival (hazard ratio = 2.45,  $p < 0.005$ ), using a cut-off as low as 1,000 ng/mL.

The authors concluded that survival and complication-free survival of patients with thalassemia major continue to improve, especially for female patients born shortly before or after the availability of iron chelation.

*(Comment: Reference is made to the fact that 32% of patients die by the age of 35 – See citation #1. For a discussion of an analogous situation, See Interactive Forum for Medical Professionals, "What are the appropriate criteria for unrelated cord blood transplantation of children with sickle cell disease.")*

4. **Beta-thalassemia.** Rund D, Rachmilewitz E. *N Engl J Med*. 2005;353:1135-46. [Extract](#)

This is a succinct **review** of  $\beta$ -thalassemia. The authors point out that thalassemia is among the most common genetic disorders worldwide. 4.83 percent of the world's population carry globin variants. The worldwide birth rate of people who are homozygous or compound heterozygous for symptomatic globin disorders, including  $\beta$ -thalassemia and  $\beta$ -thalassemia, is no less than 2.4 per 1000 births, of which 1.96 have sickle cell disease and 0.44 have thalassemias.

The authors review the clinical manifestations and supportive therapy, and emphasize that iron overload from multiple transfusions and excess gastrointestinal absorption causes most of the mortality and morbidity, although hypercoagulability is also a problem. They suggest that oral iron chelation therapy may provide significant benefits, but that long-term clinical trials are still required.

**Hematopoietic cell transplantation** is described as the only available curative therapy. They point out that low-risk patients (Lucarelli class 1 or class 2) have had excellent results after BMT (*primarily using matched, related donors*), and that outcomes using extended HLA haplotyping are similar to those using matched, related donors. They state that cord-blood transplantations have often been unsuccessful in the treatment of thalassemia because large numbers of transplanted cells need to be administered to sustain hematopoiesis and prevent graft rejection (*see comment below*). They indicate that transplantation is a viable alternative that generally results in an excellent outcome for low-risk patients.

In addition, experimental therapies are reviewed as progress in prenatal diagnosis.

*(Comment: In contrast to the authors' statement, an adequate cell dose is rather easily obtainable for cord blood transplantation of children. Since the optimal indication for transplantation in thalassemia is a low-risk patient (Lucarelli class 1 or class 2), most candidates for transplantation will be young children. Thus, cord blood transplantation including the use of cord blood units from unrelated donors is a viable option.*

*The authors cite a study of cord blood transplantation for thalassemia by Locatelli (see ii. [Thalassemia C. Umbilical Cord Blood Transplantation citation #6](#)) and imply a poor outcome. However, no patient died, and 36 of 44 children remain free of disease, with a median follow-up of 24 months (range 4-76 months). No grade III-IV acute GVHD occurred; 2 of 36 patients at risk developed limited chronic GVHD. The authors concluded that related cord blood transplantation offers a good probability of success and is associated with a low risk of GVHD. The authors also cite a report from the Peoples Republic of China in which only 4 of 9 patients became transfusion independent. However, none of the patients were Lucarelli class 1 and three of the donors were mismatched siblings (ii. [Thalassemia C. Umbilical Cord Blood Transplantation citation #5](#)).*

*For reports of successful transplantation using cord blood units from unrelated donors, see citations ii. [Thalassemia C. Umbilical Cord Blood Transplantation #1](#) and [2](#), and [citation #1](#) above.*

5. **Therapeutic options for patients with severe beta-thalassemia: the need for globin gene therapy.** Sadelain M, Boulad F, Galanello R, Giardina P, Locatelli F, Maggio A, Rivella S, Riviere I, Tisdale J. *Hum Gene Ther*. 2007;18:1-9.

The authors comment that the severe  $\beta$ -thalassemias are still debilitating, often lethal disorders, for which a **curative therapy is warranted**. Pediatric patients who have either an HLA-matched sibling or an HLA-compatible unrelated donor are candidates for allogeneic HSCT and have a high likelihood of long-term disease-free survival. They state that the remaining patients who lack an HLA-matched donor have a higher risk of mortality if they pursue partially matched HSCT using alternative donors and are at high risk of morbidity and delayed mortality if they pursue conventional supportive care. Regarding **unrelated cord blood transplantation** they quote only one reference and state that the **results are encouraging but too early and too scarce to draw definitive conclusions.** (*See [Annotated Bibliography, XII, Sickle Cell Disease and Thalassemia; ii thalassemia; C. Umbilical Cord Blood Transplantation](#)*).

Several animal models have established that correction of anemia and secondary damage is feasible using lentiviral vectors encoding a regulated human  $\beta$ -globin gene. Transfer of the normal human  $\beta$ -globin gene in autologous HSCs thus offers a rational alternative to high-risk alternative donor transplantation. The authors suggest that globin gene transfer should be tested soon in selected subjects.

The major risks of globin gene therapy are the risk of transplantation-related morbidity associated with autologous transplantation (which are less serious than the risks associated with allogeneic transplantation), and the risks associated with lentivirus-mediated globin gene transfer. The latter include insertional oncogenesis and the generation of a replication-competent lentivirus (RCL). Insertional oncogenesis has been observed previously in 3 of 22 patients in a single trial, but the risk is thought to be considerably less than that associated with the use of LTR-driven gammaretroviral vectors. The probability of RCL generation is unknown, but no replication-competent retrovirus has been reported to date in trials using gammaretrovirus or lentivirus-mediated gene transfer.

[Comment: Attempts at gene therapy in humans have proven to be disappointing in the past but offer some hope, especially for adults where the risks of allogeneic transplantation are greater than with children. For children, HSCT using stem cells from an HLA-matched sibling is a well established therapeutic modality. As more data are forthcoming, cord blood transplantation is likely to become the therapy of choice for those children without an HLA-matched sibling donor.]

6. **Genetic diseases of hemoglobin: diagnostic methods for elucidating beta-thalassemia mutations.** Tuzmen S, Schechter AN. Blood Rev. 2001;15:19-29.

The thalassemias are, worldwide, the commonest single gene disorders, causing a major public health problem especially in the Mediterranean area, the Middle East, the Indian subcontinent, the Far East, tropical Africa and the Caribbean. Nowadays, owing to the rapid population flow, they are widespread, occurring also in continental Europe, North and South America. The best available approximate estimate of affected individuals indicates that **250 million people, 4.5% of the world population, are heterozygous for a defective globin gene and that at least 300,000 lethally affected homozygotes are born annually**, approximately equally divided between thalassemias and sickle cell disorders.

The purpose of this article is to review diagnostic tools which can be used for individual diagnoses, analyses of fetal tissue, or in screening and epidemiological studies. In addition, information is provided about the most important aspects of evaluation of a patient's medical history and physical evaluation and the usual laboratory examinations that should be done in confirmation of the diagnosis. The majority of the article reviews methods for molecular diagnosis of  $\beta$ -thalassemias.

7. **Financial burden of national health insurance for treating patients with transfusion-dependent thalassemia in Taiwan.** Ho WL, Lin KH, Wang JD, Hwang JS, Chung CW, Lin DT, Jou ST, Lu MY, Chern JP. Bone Marrow Transplant. 2006;37:569-74.

**Abstract**

The mainstay of supportive treatment for transfusion-dependent thalassemia is regular blood transfusion accompanied by iron-chelating therapy. Hematopoietic stem cell transplantation (HSCT) provides an alternative option when curative therapy is considered. More than 400 patients in Taiwan have beta-thalassemia major or other transfusion-dependent thalassemias, and their treatment costs account for a considerable percentage of the National Health Insurance expenditure. The authors estimated the treatment costs of conventional therapy (regular blood transfusion accompanied by iron-chelating agents) and HSCT. The undiscounted medical cost of 20 years of follow-up (20 years from diagnosis) and the undiscounted total lifetime cost in US dollars for conventional therapy were \$149,288 and \$363,149, respectively. For HSCT costs were \$83,149 and 110,588, respectively. [Costs in New Taiwan Dollars were NT\$ 4,739,888 and NT\$ 11,529,990 for patients undergoing conventional therapy, and NT\$ 2,639,982 and NT\$ 3,511,172, respectively, for those undergoing successful HSCT.]

Comparisons of treatment costs and other parameters between these two modalities can add to the information base on which policy is made by health authorities or clinicians.

8. **Lifetime treatment costs of beta-thalassaemia major.** Karnon J, Zeuner D, Brown J, Ades AE, Wonke B, Modell B. Clin Lab Haematol. 1999;21:377-85. **Abstract**

Predictions of the costs incurred in management of patients with thalassemia major may aid health care planning. In this report, the cost to the health service of providing treatment services for beta-thalassemia major patients, over the course of a lifetime, was calculated. A cost model was developed, incorporating data from disparate sources. The undiscounted lifetime cost of treating a beta-thalassemia major patient was estimated to be £803,002 (British pounds as of publication date), although when the costs were discounted at a rate of 6%, the lifetime cost was reduced to £219,068. Within sensitivity analyses, the discounted cost ranged from approximately pound £188,000 to pound £226,000.

9. **Clinical and histological characterization of liver disease in patients with transfusion-dependent beta-thalassemia. A multicenter study of 117 cases.** Prati D, Maggioni M, Milani S, Cerino M, Cianciulli P, Coggi G, Forni GL, Magnano C, Meo A, Gramignoli R, Rebulli P, Fiorelli G, Cappellini MD; CooleyCare Cooperative Group. Haematologica. 2004;89:1179-86.

**Abstract**

The authors conducted a multicenter study within the CooleyCare Group to describe the clinical and histopathological features of liver disease in currently treated thalassemics. Two-hundred and three thalassemics with laboratory signs of liver disease were eligible. Liver biopsy was performed in the 129 (63.5%) who consented (age 26+/-7 years). Anti-hepatitis C virus (HCV) antibodies were found in 118 patients (91%), 85 (72%) of whom were viremic. Ninety-one patients (70%) had abnormal aminotransferase concentrations. In the 117 liver biopsies that met the criteria for evaluation (88%), the median Ishak's necroinflammatory and fibrosis scores were 4 (range, 0-9) and 2 (range, 0-6), respectively. Significant fibrosis (score  $\geq 3$ ) was found in 53 (45%); 9 (8%) had cirrhosis. At multivariate analysis, necroinflammation was related to HCV viremia, and fibrosis to increased serum aminotransferases, higher iron stores (including serum ferritin, Deugnier's total iron score, and liver iron content) and male gender ( $p < 0.05$ ). In HCV-RNA negative subjects, the median total iron score was 27 (range, 0-52). Iron accumulated in both mesenchymal cells and hepatocytes, and the presence of a lobular gradient was interpreted to indicate intestinal hyperabsorption.

The authors concluded that transfusion-dependent thalassemics have mild liver necroinflammation, mainly attributable to HCV infection. Significant fibrosis is frequent, and its progression is mostly influenced by iron overload which, with current therapy regimens, may be attributable to both erythrocyte catabolism and iron hyperabsorption.

10. **Severe infections in thalassaemic patients: prevalence and predisposing factors.** Rahav G, Volach V, Shapiro M, Rund D, Rachmilewitz EA, Goldfarb A. Br J Haematol. 2006;133:667-74. **Abstract**

The incidence of infections among patients with thalassaemia and the role of risk factors for infection are uncertain. The investigators studied the occurrence of infections necessitating hospitalization in 92 homozygous beta-thalassaemia patients who had been followed longitudinally for decades, and investigated the role of potential risk factors for these infections.

Pneumonia accounted for 26% of the infections and fever of unknown origin for 14%. Staphylococcus aureus was the major pathogen possibly related to injections associated with intensive chelation with deferoxamine. There was a significant increase in the rate of infection over time, notably after 15 years. Splenectomy correlated with the incidence of infection ( $P < 0.001$ ) without being confounded by other variables and with highest frequencies of infections present after 10 years. A direct correlation between iron overload and infection was evident only before the initiation of iron-chelating treatment ( $P < 0.01$ ). Following initiation of deferoxamine, paradoxically, the infection rate increased ( $P = 0.046$ ). The combination of splenectomy and deferoxamine treatment was associated with the highest adjusted infection rate. Parathyroid dysfunction and glucose-6-phosphate dehydrogenase deficiency were significantly associated with infection ( $P = 0.02$  and  $P = 0.04$  respectively).

The authors concluded that the infection rate in thalassaemia is affected mainly by the duration of the disease and is increased by splenectomy and, in the long term, by treatment with deferoxamine.

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3 June 2007

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