Community public health issues and the thalassemic syndromes: Lessons from other countries

Author
Stanley L Schrier, MD

Section Editor
William C Mentzer, MD

Deputy Editor
Stephen A Landaw, MD, PhD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Jan 2015. | **This topic last updated:** Nov 20, 2014.

INTRODUCTION — Beta thalassemia occurs in the Mediterranean littoral and all over Southeast Asia (Burma, Thailand, Cambodia, Vietnam, China, Malaysia, Indonesia, and the Philippines). Alpha thalassemia is even more common, occurring with high frequency throughout all tropical and subtropical regions, including most of Southeast Asia, the Mediterranean area, the Indian subcontinent, the Middle East, and Africa [1,2].

Some variants of thalassemia (eg, hydrops fetalis with hemoglobin Bart's) are incompatible with life [3], while others (eg, beta thalassemia major) are associated with lifelong transfusion-dependent anemia, short stature, facial abnormalities, delayed or absent puberty, and attendant stigmas and psychosocial problems [4,5].

Of major public health importance, individuals with one of the various forms of thalassemia trait may be entirely asymptomatic, unaware of their diagnosis, and procreate with other individuals with the same trait, thereby perpetuating the disorder within these communities. (See "Clinical manifestations and diagnosis of the thalassemias".)

An interesting anecdote illustrates our changing perceptions about these disorders. Thalassemia was not diagnosed in Cyprus before 1944 [1]. After World War II, following improvements in public health along with malarial eradication programs, it became apparent that there was a newly recognized but common hypochromic microcytic anemia in children not due to iron deficiency (ie, severe beta thalassemia) [4]. It was quickly realized that, for example, the cost of red blood cell transfusions and chelation therapy per year for a patient with beta thalassemia major exceeded by three to four orders of magnitude the per capita funds available for health care in that country, as well as in much of the developing world.

By 1970, it was projected that, if this disease was not controlled, by the year 2000 the cost of treatment of these children would consume the entire health care budget of Cyprus and require all of the blood that the island could supply, even supposing that 40 percent of the adults would enlist as regular blood donors.

In the past, in many of the underdeveloped nations, at a time when the infant mortality rate was above 50/1000 births, affected countries devoted their public health efforts to controlling neonatal infectious diseases and malnutrition. Thus, of the well over 300,000 infants with major forms of severe hemoglobin disorders, including the thalassemias, who were born every year, many died untreated or even undiagnosed [4]. However, when the infant mortality rate fell below 40/1000, genetic diseases such as the thalassemias "emerged," along with a demand for appropriate medical services [4], as occurred in Cyprus.

SEVERE THALASSEMIA IN THE DEVELOPED WORLD — Before 1980, hemoglobin E (HbE) was not recognized in California [6]. Now that the California population is 10 percent Asian, the number of children born with thalassemia has been increasing. As a result, the number of births in California of children with homozygous HbE disease now exceeds the number of births of children with sickle cell disease. In addition, there are now 11 new cases of HbE/beta thalassemia per year, as well as 30 new cases per year of HbH disease (severe alpha thalassemia) [6,7]. Other examples include:

- In the United Kingdom (UK), there are now more than 50 patients with severe HbE/beta thalassemia, mostly of Bengali or Southeast Asian origin [8].

- A 1998 lead article in the journal "Blood" dealt with an emerging health care problem due to an increased frequency of stillbirths secondary to severe alpha thalassemia (ie, hydrops fetalis with hemoglobin Bart's) [3]. The article came not from China, Singapore, or Hong Kong, where this syndrome had been well described, but from Ontario, Canada [3]. Similar experience from Boston, Massachusetts has been reported [9].

The demographics in these three countries (UK, Canada, United States) have obviously changed [10,11]; simple arithmetic indicates that many patients with thalassemia have not been diagnosed and/or appropriately treated, and that there is clearly a need to improve community education programs, as well as opportunities for genetic and prenatal counseling.

With increasing population movements, combinations of the various thalassemias and hemoglobinopathies are expected to increase. Towards that end, interactions between "source" areas (ie, those with a high prevalence of alpha thalassemia and substantial emigration) and "sink" areas (ie, those with substantial immigration from source areas) have developed [2]. Examples include collaborations between the Philippines and California and between Sri Lanka and the UK [12,13].

EFFECTIVE CONTROL OF THALASSEMIA — Control of thalassemia requires treatment of the individual patient as well as a community-based educational effort to increase awareness of this problem.

Individual patients — Other than the use of transfusion and general supportive care, there is no effective treatment for the vast majority of individuals with severe forms of alpha thalassemia. In addition, the hemoglobin Bart's hydrops fetalis syndrome, which is almost universally fatal for the fetus or newborn, is often accompanied by a variety of maternal complications, which may be fatal. Accordingly, programs for prevention of these disorders, and early detection during pregnancy, assume major importance [2,14].

For individual patients with beta thalassemia major, appropriate treatment includes all of the following (see "Treatment of beta thalassemia") [1,4,15,16]:

- Lifelong red cell transfusions
- Control of the blood supply to avoid transfusing hepatitis and HIV
- Chelation programs to minimize transfusional iron overload
- Prompt treatment of all infections
- Treatment of endocrine complications related to iron overload, including hormone supplementation to allow normal puberty and growth
- Splenectomy when and if hypersplenism occurs
- Control of osteoporosis

Hematopoietic cell transplantation — If the patient with beta thalassemia major has an HLA-matched sibling hematopoietic cell donor (approximately 30 percent of patients), lives in an affluent country, and/or has the financial resources, an allogeneic hematopoietic cell transplantation (HCT) is essentially curative in 80 percent or more of such patients. In response to this need, the HCT program in Pesaro, Italy has completed over 1000 such transplants. (See "Efficacy of hematopoietic cell transplantation in beta thalassemia major".)

If non-myeloablative HCT is successful in thalassemia [17], it would be possible in the wealthier countries to extend transplantation to partially matched donors. However, this is not a solution for most of the developing world. Unrelated donor HCT has also been used in severely affected adult patients, but only if the potential candidates are rigidly screened and fully informed about the risks of this procedure [18]. (See "Specific issues related to hematopoietic cell transplantation in beta thalassemia", section on 'Persistent mixed chimerism' and "Preparative regimens for hematopoietic cell transplantation", section on 'Nonmyeloablative and reduced intensity preparative regimens'.)

Improved diagnostic and screening methods — The underlying cause of the defective and deficient globin chain synthesis in the thalassemias has been explored. For the beta thalassemias, most are problems in gene transcription, while for the alpha thalassemias, gene deletions are the usual cause. Using reliable probes, it is now

possible to screen populations for these defects. Despite the vast heterogeneity of these disorders, it has turned out in practice that in each given geographic and ethnic area there is a reproducible pattern of recurrent abnormalities, such that diagnostic accuracy can be achieved using relatively small numbers of probes [1,19]. (See "Laboratory diagnosis of the hemoglobinopathies".)

The effectiveness and difficulties of screening is illustrated in a report from Indonesia where issues of education, awareness of the disorder, and stigmatization emerged [20].

Search for an orally active iron chelating agent — Development of a cheap, orally-effective iron chelator is an additional biologic intervention that would dramatically reduce costs and increase the effectiveness of available medical treatment of thalassemia. Deferiprone is in widespread use. An orally active tridentate iron chelator, deferasirox, which can be given once daily, has been approved for use in the United States. Long-term benefits of both agents are under intensive study. (See "Chelation therapy for thalassemia and other iron overload states".)

Biological problems — It was originally thought that HbE/beta thalassemia [8], HbH disease, and HbH/Constant Spring is more severe in the developing world because of the existence of comorbid conditions such as malaria, other infectious disease, contaminated water, and malnutrition. However, preliminary data indicate that patients with HbE/beta thalassemia and HbH are as anemic in the United Kingdom and Oakland, California as they are in Thailand.

Financial problems — Transfusion support requires a blood procurement program that has appropriate storage capacity, excellent donor identification, and the capability of screening for blood-borne infections, such as hepatitis and HIV. These screening tests are sophisticated and expensive. The problems of supporting the medical needs of these patients fall primarily on local programs in developed countries.

Community-wide problems — Understanding the molecular and genetic basis of the thalassemias has allowed us to apply this information to communities and entire countries [4]. As examples, the frequency of the hemoglobin Constant Spring (HbCS) gene in Bangkok is 8 percent, the frequency of the HbE trait in the Southeast Asian triangle is 40 to 60 percent, while the frequency of the alpha thalassemia trait in Melanesia and parts of Nepal have reached 70 and 90 percent, respectively [21,22].

Genetic counseling of couples — To be clinically useful, this screening information has to be coupled with an education program informing local physicians and the affected population about the disease, its manifestations, cause, and clinical course. Following this, there must be accessible opportunities for genetic counseling. As an example, if both parents have beta thalassemia trait, they can be told the following about the chances of an affected child:

- Child with severe disease (beta thalassemia major) – One chance in four
- Asymptomatic carrier (beta thalassemia trait) – One chance in two
- Unaffected child – One chance in four

Genetic counseling has generally had little or no impact on the choice of spouse, although separating and finding another spouse was a major option in Iran before prenatal testing was generally available and abortion of an affected fetus was permitted by the government [23]. On the other hand, once pregnancy has occurred, given that community educational programs have been effective, the couple will almost invariably seek prenatal diagnosis, which can be achieved before 13 weeks, using chorionic villus biopsy [4]. (See "Prenatal screening and testing for hemoglobinopathy", section on 'Prenatal diagnosis'.)

Depending on the ethnic group and the society, the couple then has an opportunity to choose whether to terminate or continue the pregnancy [23]. As an example, in Cyprus, Sardinia, Italy, and Greece [4], when the couple has been informed that the fetus is affected with beta thalassemia major, over 97 percent of the couples terminated the pregnancy (table 1) [24].

A pilot hospital-based screening and education program on the southeastern coast of China has had similar success [25]. Over an 11-year period from 1993 through 2003, 4587 out of 49,221 screened pregnant women were

found to be carriers of alpha or beta thalassemia. Ninety-eight percent of the partners of these women agreed to screening, and 281 of the couples were found to be at risk for severe thalassemia. Prenatal diagnosis was performed in 269 (95.7 percent) of the 281 at-risk pregnancies, which identified 69 severely affected fetuses (25.6 percent). All pregnancies with severely affected fetuses were voluntarily terminated.

During this time there were only two affected children born at this large regional hospital, both with homozygous alpha (0) thalassemia. These children were from the 12 couples that refused to accept prenatal diagnosis.

Ethical issues — An important question that has arisen is whether it is ethical to provide prenatal screening services designed to detect fetal abnormalities, such as alpha or beta thalassemia major, without providing increased access to abortion. As an example, Iran has tackled this issue by liberalizing its abortion laws for fetuses with thalassemia [26]. Other major ethical issues include the following [27]:

- The techniques for preimplantation genetic diagnosis and therapy have been developed for single gene disorders, such as the thalassemias. These techniques might be employed by a couple at risk in order to select an uninvolved embryo for implantation. (See "Prenatal screening and testing for hemoglobinopathy", section on 'Prenatal diagnosis'.)

- These techniques might also be employed by a family that had a severely affected child with thalassemia major, but no HLA-matched sibling donor for a curative allogeneic hematopoietic cell transplantation (HCT). Through the use of these single cell genetic methods, the parents' fertilized eggs might be screened to select one that is not thalassemic and is also HLA compatible with the affected child [28,29]. This fertilized egg is then implanted in the mother, and, at the time of delivery, cord blood stem cells are harvested for use in the subsequent allogeneic HCT for the affected child.

Clearly, there are very important ethical and financial issues involved in these two scenarios. (See "Hematopoietic cell transplantation for idiopathic severe aplastic anemia and Fanconi anemia in children and adolescents", section on 'Use of umbilical cord blood for transplantation'.)

IMMIGRATION PATTERNS AND PROVISION OF HEALTH CARE — In the individual Mediterranean countries such as Greece and Italy, there is a commonality of language, culture, and religion, and there are strong state-supported health care systems. However, with current immigration patterns, Southeast Asians are now being cared for in countries with different languages, cultural norms [4,5,30], and health care systems. This has led to a number of problems in education occurring at several different, but interrelated, levels.

Physician education — Few physicians in the United Kingdom, Canada, and the United States have experience caring for patients with severe thalassemia. This care requires knowledgeable physicians with the requisite diagnostic facilities, including relevant molecular biologic probes; laboratory and transfusion support; and knowledge about stunted growth, endocrine disorders, bone disease, facial deformities, delayed puberty, and management of infections, splenomegaly, and viral hepatitis.

Thus, physicians in communities of the developed world to which Southeast Asians have immigrated must be trained in all of the above subjects. Furthermore, since patients with severe thalassemia are surviving into their 30s and 40s, other changes have to occur [31]:

- Physicians who care primarily for adults and are currently inexperienced in caring for thalassemics must be taught to care for these patients, **or**

- Pediatricians, the traditional caregivers of the past, will have to continue to take care of such patients well after the onset of puberty.

Translators and nurse practitioners — In the short term, ensuring effective communication between the affected families, community facilities, and the medical community requires the provision of adequate numbers of language translators and appropriate community role models, such as nurse practitioners and other health care providers of the same ethnic background [30].

Community educational programs — The community and its leaders must be educated about these diseases, options for management, and the available facilities. Community leaders, in turn, must ensure that opportunities exist for locally obtaining the necessary genetic counseling, prenatal testing, and appropriate medical care.

The most effective intervention thus far has been population screening to identify ethnic-specific patterns of molecular abnormalities, genetic counseling combined with highly reliable prenatal diagnosis, followed by community and social support that allows the affected couple to choose to act on the information and terminate an affected pregnancy [1,4,5,32-34]. While such molecular diagnostic programs are expensive, they are remarkably cost-effective, as demonstrated in Cyprus, Sardinia, Italy, and Greece [1,4,32].

Examples of effective community action — The experience of three countries has given us a clear description of an optimal support system [5,35,36].

Greece — There are 3500 patients with severe beta thalassemia major in Greece, who consume one-quarter of the country's total blood supply. Iron chelation therapy alone costs 7 million dollars per year. Accordingly, Greece has generated an extensive educational program to produce public awareness. This is coupled with easy access to a program of prenatal diagnosis and screening, along with a very extensive social support program (table 2) [5]. Considering the ongoing financial crisis in Greece, it is not clear which, if any, of these benefits persist.

Parent groups have been encouraged to the extent that 90 percent of thalassemic patients use the support system and are aware of the issues surrounding this disorder (table 3) [5]. Psychosocial support is also provided as an integral part of this scheme, such that the psychosocial burden has changed significantly (table 4 and table 5) [5]. It would be difficult to envision a more extensive and comprehensive program. As a direct result of this effort, the average age of beta thalassemia major patients in Greece is now 27, and very few new patients with beta thalassemia major are being born (figure 1) [5].

Italy — A very similar program, although not quite so extensive, is provided in Italy by the Pediatric Program in Ferrara, which cares for 170 patients with beta thalassemia major [35]. The key to the Ferrara Program is outpatient care and a strong parent association. However, no psychiatric or social support is provided [35].

A study compared the 170 Ferrara patients with 300 patients in the Athens thalassemia program. Surprisingly, the psychosocial adjustment in Ferrara, when formally assessed, was better than that in Athens, where there was considerable hostility and only 30 percent of patients were compliant with chelation therapy. It has been stated that "Illness dominates all aspects of life" in Athens, but not in Ferrara [5,35]. In Ferrara, adjustment was good, even leading to marriage and families, with the social support being provided mainly by the family and its religion. One wonders whether the maximal program in Greece has led to unrealistic expectations.

Cyprus — Before 1976, the birth rate for severe thalassemia in northern Cyprus was 18 to 20 cases per year. The following actions were taken to reduce this serious health problem [36]:

- Screening high-risk families for thalassemia was started in 1979
- Premarital screening was made compulsory in 1980
- Prenatal diagnosis with fetal blood sampling was started in 1984
- DNA techniques replaced fetal blood sampling in 1991
- Facilities were provided for treatment of existing thalassemic patients

As a result of these actions, the birth rate for severe thalassemia between 1991 and 2001 had dropped to one case every two to three years, and there were no such births during the following five years. Two-thirds of the existing patients with severe thalassemia are now >25 years of age, living and working in the same way as the normal population; 38 percent are married with children.

China — The exact number of cases of thalassemia in China is not known, but it is clear that this disease strains health resources in that country. To ease this burden, the Chinese government has embarked on a comprehensive prevention program featuring population screening, prenatal diagnosis, and genetic research funding,

with a goal to do as well as the program initiated in Cyprus [37].

The cost-benefit ratio of an alpha thalassemia prevention program has been conducted in Hong Kong, and has concluded that universal prenatal screening for the alpha and beta thalassemias with the use of DNA testing is cost-effective [38].

Other countries — Cost-benefit analyses of beta thalassemia programs in Quebec, Iran, Israel, and the United Kingdom have generally confirmed the overall benefits of such programs, in that the costs of prevention were lower than the costs of treatment [2,39-43].

COMPONENTS OF A SUCCESSFUL PROGRAM — There is certainly a need to educate physicians about this disease and its management, as well as to have an explicit local, regional, and national policy to cover antenatal and prenatal screening for these hemoglobinopathies [44]. It is, however, critical to inform and empower the affected ethnic groups now living in the developed world. (See "Prenatal screening and testing for hemoglobinopathy", section on 'Prenatal diagnosis'.)

The Oakland, California group has found that language translators and nurse practitioners from the affected ethnic groups are very important for the success of these programs. Contact also needs to be made with community leaders to educate, inform, and involve them in community educational programs. Weekly meetings among patients, parents, community leaders, and the medical staff to discuss issues and problems are of paramount importance. Other effective programs would include special family nights, health fairs, and language-specific literature, including information concerning subjects such as genetic counseling, prenatal diagnosis, intercurrent illness, sexual development, pregnancy, and osteopenia [6,30,31,45,46].

SUMMARY AND RECOMMENDATIONS

- Problem overview – Beta thalassemia occurs in the Mediterranean littoral and all over Southeast Asia (Burma, Thailand, Cambodia, Vietnam, China, Malaysia, Indonesia, and the Philippines). Alpha thalassemia is even more common, occurring with high frequency in Southeast Asia, Africa, and India. A number of issues concerning thalassemia have important public health implications in these countries as well as in the developed world. These include the following (see 'Introduction' above and 'Severe thalassemia in the developed world' above):
    - By 1970, it was projected that, if thalassemia was not controlled in Cyprus, by the year 2000 the cost of treatment of these children would consume the entire health care budget of Cyprus and require all of the blood that the island could supply.
    - There are 3500 patients with severe beta thalassemia major in Greece, who consume one-quarter of the country's total blood supply. Iron chelation therapy alone costs 7 million dollars per year.
    - Before 1980, hemoglobin E (HbE) was not recognized in California. Now that the California population is 10 percent Asian, the number of children born with thalassemia has been increasing. As a result, the number of births in California of children with homozygous HbE disease now exceeds the number of births of children with sickle cell disease.
    - In the individual Mediterranean countries, such as Greece and Italy, there is a commonality of language, culture, and religion, and there are strong state-supported health care systems. However, with current immigration patterns, Southeast Asians are now being cared for in countries with different languages, cultural norms, and health care systems.
- Potential solutions – Solution of the above problems requires action on all of the following levels (see 'Components of a successful program' above and 'Examples of effective community action' above):
    - Education of health care providers (see 'Physician education' above and 'Translators and nurse practitioners' above)

- Effective community educational programs (see 'Community educational programs' above)
- Effective counseling of couples at risk of having an affected child (see 'Genetic counseling of couples' above)

REFERENCES

1. Weatherall DJ. Thalassemia in the next millennium. Keynote address. Ann N Y Acad Sci 1998; 850:1.
2. Piel FB, Weatherall DJ. The α-thalassemias. N Engl J Med 2014; 371:1908.
3. Chui DH, Waye JS. Hydrops fetalis caused by alpha-thalassemia: an emerging health care problem. Blood 1998; 91:2213.
4. Angastiniotis M, Modell B. Global epidemiology of hemoglobin disorders. Ann N Y Acad Sci 1998; 850:251.
5. Politis C. The psychosocial impact of chronic illness. Ann N Y Acad Sci 1998; 850:349.
6. Lorey F, Cunningham G. Impact of Asian immigration on thalassemia in California. Ann N Y Acad Sci 1998; 850:442.
7. Vichinsky EP. Clinical manifestations of α-thalassemia. Cold Spring Harb Perspect Med 2013; 3:a011742.
8. Rees DC, Styles L, Vichinsky EP, et al. The hemoglobin E syndromes. Ann N Y Acad Sci 1998; 850:334.
9. Chui DH, Cunningham MJ, Luo HY, et al. Screening and counseling for thalassemia. Blood 2006; 107:1735.
10. Luo HY, Boudreaux J, Steinberg MH, Chui DH. Patients with thalassemia in the United States. Blood 2005; 105:4896.
11. Vichinsky EP, MacKlin EA, Waye JS, et al. Changes in the epidemiology of thalassemia in North America: a new minority disease. Pediatrics 2005; 116:e818.
12. Padilla CD, Therrell BL. Newborn screening in the Asia Pacific region. J Inherit Metab Dis 2007; 30:490.
13. de Silva S, Fisher CA, Premawardhena A, et al. Thalassaemia in Sri Lanka: implications for the future health burden of Asian populations. Sri Lanka Thalassaemia Study Group. Lancet 2000; 355:786.
14. Higgs DR. alpha-Thalassaemia. Baillieres Clin Haematol 1993; 6:117.
15. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and disease complications in thalassemia major. Ann N Y Acad Sci 1998; 850:227.
16. Hershko C, Link G, Cabantchik I. Pathophysiology of iron overload. Ann N Y Acad Sci 1998; 850:191.
17. Storb R, Yu C, Deeg HJ, et al. Current and future preparative regimens for bone marrow transplantation in thalassemia. Ann N Y Acad Sci 1998; 850:276.
18. Caocci G, La Nasa G, d'Aloja E, et al. Ethical issues of unrelated hematopoietic stem cell transplantation in adult thalassemia patients. BMC Med Ethics 2011; 12:4.
19. Yin A, Zhang L, Luo M, et al. Development of bead-based suspension array technology for the diagnosis of thalassemia. Am J Hematol 2014; 89:1158.
20. Widayanti CG, Ediati A, Tamam M, et al. Feasibility of preconception screening for thalassaemia in Indonesia: exploring the opinion of Javanese mothers. Ethn Health 2011; 16:483.
21. Flint J, Hill AV, Bowden DK, et al. High frequencies of alpha-thalassaemia are the result of natural selection by malaria. Nature 1986; 321:744.
22. Modiano G, Morpurgo G, Terrenato L, et al. Protection against malaria morbidity: near-fixation of the alpha-thalassemia gene in a Nepalese population. Am J Hum Genet 1991; 48:390.
23. Samavat A, Modell B. Iranian national thalassaemia screening programme. BMJ 2004; 329:1134.
24. Beris P, Darbellay R, Extermann P. Prevention of beta-thalassemia major and Hb Bart's hydrops fetalis syndrome. Semin Hematol 1995; 32:244.

25. Liao C, Mo QH, Li J, et al. Carrier screening for alpha- and beta-thalassemia in pregnancy: the results of an 11-year prospective program in Guangzhou Maternal and Neonatal hospital. Prenat Diagn 2005; 25:163.
26. Ballantyne A, Newson A, Luna F, Ashcroft R. Prenatal diagnosis and abortion for congenital abnormalities: is it ethical to provide one without the other? Am J Bioeth 2009; 9:48.
27. Yurkiewicz IR, Korf BR, Lehmann LS. Prenatal whole-genome sequencing--is the quest to know a fetus's future ethical? N Engl J Med 2014; 370:195.
28. Fiorentino F, Biricik A, Karadayi H, et al. Development and clinical application of a strategy for preimplantation genetic diagnosis of single gene disorders combined with HLA matching. Mol Hum Reprod 2004; 10:445.
29. Verlinsky Y, Rechitsky S, Sharapova T, et al. Preimplantation HLA testing. JAMA 2004; 291:2079.
30. Choy J, Yamashita RC, Foote D, et al. Outreach strategies for Asian Pacific Island (API) communities. Ann N Y Acad Sci 1998; 850:514.
31. Weissman L, Treadwell M, Foote D, et al. Approaches to working with adult thalassemia patients in pediatric settings. Ann N Y Acad Sci 1998; 850:516.
32. Weatherall DJ, Clegg JB. Thalassemia--a global public health problem. Nat Med 1996; 2:847.
33. Ahmed S, Saleem M, Modell B, Petrou M. Screening extended families for genetic hemoglobin disorders in Pakistan. N Engl J Med 2002; 347:1162.
34. Cao A, Galanello R. Effect of consanguinity on screening for thalassemia. N Engl J Med 2002; 347:1200.
35. Di Palma A, Vullo C, Zani B, Facchini A. Psychosocial integration of adolescents and young adults with thalassemia major. Ann N Y Acad Sci 1998; 850:355.
36. Bozkurt G. Results from the north cyprus thalassemia prevention program. Hemoglobin 2007; 31:257.
37. Hvistendahl M. Genetic disease. China heads off deadly blood disorder. Science 2013; 340:677.
38. Leung KY, Lee CP, Tang MH, et al. Cost-effectiveness of prenatal screening for thalassaemia in Hong Kong. Prenat Diagn 2004; 24:899.
39. Ostrowsky JT, Lippman A, Scriver CR. Cost-benefit analysis of a thalassemia disease prevention program. Am J Public Health 1985; 75:732.
40. Ahmadnezhad E, Sepehrvand N, Jahani FF, et al. Evaluation and cost analysis of national health policy of thalassaemia screening in west-azerbaijan province of iran. Int J Prev Med 2012; 3:687.
41. Ginsberg G, Tulchinsky T, Filon D, et al. Cost-benefit analysis of a national thalassaemia prevention programme in Israel. J Med Screen 1998; 5:120.
42. Koren A, Profeta L, Zalman L, et al. Prevention of β Thalassemia in Northern Israel - a Cost-Benefit Analysis. Mediterr J Hematol Infect Dis 2014; 6:e2014012.
43. Zeuner D, Ades AE, Karnon J, et al. Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis. Health Technol Assess 1999; 3:i.
44. Streetly A. A national screening policy for sickle cell disease and thalassaemia major for the United Kingdom. Questions are left after two evidence based reports. BMJ 2000; 320:1353.
45. Heer N, Choy J, Vichinsky EP. The social impact of migration on disease. Cooley's anemia, thalassemia, and new Asian immigrants. Ann N Y Acad Sci 1998; 850:509.
46. Garofalo F, Piga A, Lala R, et al. Bone metabolism in thalassemia. Ann N Y Acad Sci 1998; 850:475.

Topic 7117 Version 10.0

GRAPHICS

Results of fetal DNA testing for thalassemia major syndromes, June 1974 - December 1989

Parameter	Number of cases	Percent
Total cases at risk for thalassemia	4300	
Affected cases	1074	25.0
Pregnancies continued	29	2.7
Fetal losses	-	1.2*
Diagnostic errors	-	0.5*

* Data from 6300 cases tested for either thalassemia or sickle cell disease.

Reproduced with permission from: Beris P, Darbellay R, Extermann P. Prevention of beta-thalassemia major and Hb Bart's hydrops fetalis syndrome. Semin Hematol 1995; 32:244.

Graphic 82751 Version 5.0

Social benefits provided to thalassemic patients in Greece

Free medical care
Cash benefits
Tax allowances
Entry to universities and other institutions of higher education without examination
Paid training and technical education
Work incentives (large industries are obliged to employ disabled people up to 4 percent of their labor force)
Early retirement
Facilities (eg, transportation, electricity, telephone)

Data from: Politis C. The psychosocial impact of chronic illness. Ann N Y Acad Sci 1998; 850:349.

Graphic 79598 Version 2.0

Public awareness of thalassemia

93 percent were aware of thalassemia
90 percent were aware of the need for blood transfusion
89 percent knew that thalassemia is not infectious
80 percent knew about the hereditary nature of thalassemia
69 percent believed that thalassemia is presently incurable

Number interviewed: 3478.

Data from: Politis C. The psychosocial impact of chronic illness. Ann N Y Acad Sci 1998; 850:349.

Graphic 78796 Version 2.0

Psychosocial burden of thalassemia in the past

Stigmatization
Secrecy about the illness
Isolation of patient and family
Physical handicap
Absence of sexual development
Fear of dying before adulthood
Fear of social rejection
Dependency

Data from: Politis C. The psychosocial impact of chronic illness. Ann N Y Acad Sci 1998; 850:349.

Graphic 62593 Version 2.0

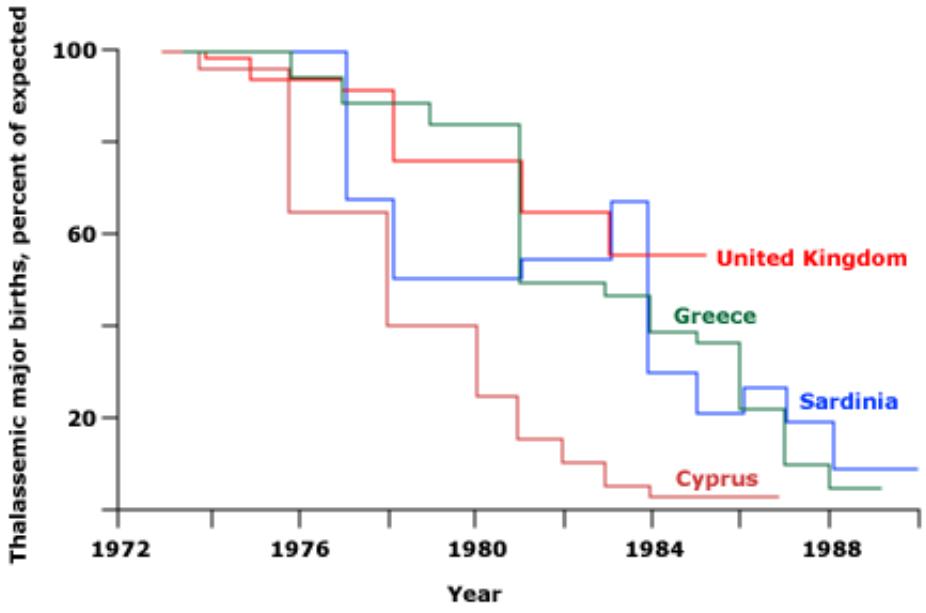
Psychosocial burden of thalassemia in the present

Better physical appearance
Pubertal growth and sexual development
Schooling
Working
Establishing relationships
Getting married
Raising a family
Low compliance with treatment for large number of patients
Living for today
Denial/anxiety/hostility
Prospects
Oral chelators
HbF inducers
Bone marrow transplantation
Gene therapy

Data from: Politis C. The psychosocial impact of chronic illness. Ann N Y Acad Sci 1998; 850:349.

Graphic 76407 Version 2.0

Change in birth rate of thalassemic children after the introduction of preventive programs



Data from: Cao A, Galanello R, Rosatelli MC, et al. Clinical experience of management of thalassemia: the Sardinian experience. Semin Hematol 1996; 33:66.

Graphic 65994 Version 2.0

Disclosures

Disclosures: **Stanley L Schrier, MD** Nothing to disclose. **William C Mentzer, MD** Equity Ownership/Stock Options: Johnson & Johnson [Anemia (Erythropoietin)]. **Stephen A Landaw, MD, PhD** Employment (Spouse): Mass Medical Society (New England Journal of Medicine).

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy