health technology

REP ORT

MANAGEMENT OF THALASSAEMIA

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EXECUTIVE SUMMARY

1. BACKGROUND

Thalassaemias and Sickle cell disorder, are the commonest human inherited haemoglobin disorders that can be treated effectively, and also prevented at community level.
Thalassaemia is the commonest single gene disorder in Malaysia and a paradigm of monogenetic diseases. In 1995, it was estimated that about 8,000 persons were afflicted with HbE beta Thalassaemia, and 8,000 with Homozygous beta-Thalassaemia, about 40% of whom were dependent on regular blood transfusions for survival (Kaur, 1995). In addition, the carrier rate for beta Thalassaemia and HbE is estimated to be 3-5%.
Besides blood transfusion, another curative option is the use of haemopoietic stem cell transplantation. In Malaysia, it is currently being offered to potential patients with suitable donors at two centres, namely, University Malaya Medical Centre and the Paediatrics Institute, Kuala Lumpur Hospital.

2 OBJECTIVE

To determine the safety, effectiveness, cost implications as well as ethical, legal and social implications of management of Thalassaemia.

3. SCOPE

This assessment does not include diagnosis of Thalassaemia, as well as antenatal screening for Thalassaemia that has already been assessed previously under antenatal screening.

4. RESULTS

There is sufficient evidence that a screening and prevention programme is effective for the control of β-thalassaemia trait. The options for effective screening include screening of 15-16 year old school students, pre-marital screening, and screening of relatives of known carriers. Screening tests include MCH and osmotic fragility test.
The complications of Thalassaemia include Hepatitis B and Hepatitis C, cardiac complications like heart failure, short stature, pubertal delay, and osteoporosis. Other less common complications include diabetes mellitus.
With respect to blood transfusion, there is sufficient evidence to conclude that leukocyte reduced red cells, produced either in the blood bank or using bed-side filters, are effective in reducing transfusions reactions, the better the filter, the greater the reduction in transfusion reactions. The use of neocytes for transfusion can decrease blood requirement, but is costly.
For the treatment of Thalassaemia by chelation therapy, there is sufficient evidence that Desferrioxamine and Deferiprone are effective in preventing or improving serious complications of the disease.
There is sufficient evidence that sibling donor bone marrow transplantation is safe and effective, and more cost effective compared to blood transfusion therapy. There is also evidence of effectiveness of bone marrow transplantation from unrelated and alternative donors, cord blood transplantation and peripheral blood stem cell transplantation.
Modulators of fetal hemoglobin synthesis like Hydroxyurea, Butyrates, 5 Azacytidine and Erythropoietin is still largely experimental and cannot replace the need for regular blood transfusions and regular chelation therapy. Gene therapy to replace bone marrow transplant seems to be possible.
There is insufficient evidence on the effectiveness of other treatment modalities like nutrition support and vitamins.

5. RECOMMENDATION

It is recommended that a screening and prevention programme for the control of β-thalassaemia trait be instituted. Screening of school students and screening of relatives of known carriers should be carried out. Pre-marital and prenatal screening services should be offered for those who request for it.

Thalassaemic children on blood transfusion should receive leukocyte-reduced red cells for. All blood should be screened for ABO and Rh (D) compatibility, while Rh (C and E) and Kell is not recommended because of high cost involved.

For Chelation therapy, it is recommended that Desferrioxamine and Deferiprone be used to prevent or improve serious complications of the Thalassaemia.

Bone Marrow Transplantation should be offered to patients as soon as possible especially if there is a HLA compatible sibling/ family member. Bone marrow transplantation from unrelated and alternative donors, cord blood transplantation and peripheral blood stem cell transplantation services can also be offered where indicated.

There is insufficient evidence to recommend other treatment modalities.

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MANAGEMENT OF THALASSAEMIA

1. BACKGROUND

Thalassaemias and Sickle cell disorders, are the commonest human inherited haemoglobin disorders that can be treated effectively, and also prevented at community level. Haemoglobin disorders occur in most countries of the world due to global migration, and are emerging as health problems in developing countries.

Thalassaemia is the commonest single gene disorder in Malaysia and a paradigm of monogenetic diseases. In 1995, it was estimated that about 8,000 persons were afflicted with HbE beta Thalassaemia, and 8,000 with Homozygous beta-Thalassaemia, about 40% of whom were dependent on regular blood transfusions for survival (Kaur, 1995). In addition, the carrier rate for beta Thalassaemia and HbE is estimated to be 3-5%, with about 120-350 new patients born each year. Since there is no national screening policy, national Thalassaemia trait (carrier) registry or registry of beta Thalassaemia major patients, the current figures available are presumptive, derived from population studies data of various research workers in the country. Based on an estimated population of 22.7 million, the number of cases afflicted with beta Thalassaemia major among Malays and Chinese are 4 380, with 2 140 HbE beta Thalassaemia cases among Malays. Each year there are an estimated 46 births of beta-Thalassaemia major. Sabah appears to have a higher incidence of Thalassaemia major, with 676 cases registered with the Thalassaemia Association of Sabah.

Besides blood transfusion, another curative option is the use of haemopoietic stem cell transplantation. The first patient with Thalassaemia was successfully transplanted with allogenic marrow in Seattle in 1981. In Pesaro, Italy, of the 800 bone marrow transplants carried out over the last 20 years, a survival rate of 95 % has been reported in patients with no hepatomegaly, minimal liver fibrosis and a good history of previous iron chelation. (Lucarelli,1999). In Malaysia, it is currently being offered to potential patients with suitable donors at two centres, namely, University Malaya Medical Centre and the Paediatrics Institute, Kuala Lumpur Hospital.

2 OBJECTIVE

To determine the safety, effectiveness, cost implications as well as ethical, legal and social implications of management of Thalassaemia

4. SCOPE

This assessment does not include diagnosis of Thalassaemia, as well as antenatal screening for Thalassaemia that has already been assessed previously under antenatal screening.

5. TECHNICAL FEATURES

4.1 Screening Program

Screening and prevention for Thalassaemia entails screening for carriers in the community, genetic counselling, providing facilities for prenatal diagnosis with an option for termination of

pregnancy, if the fetus is found to have Thalassaemia major and a dedicated screening approach targeting couples at marriage and early pregnancy has been found to be very effective. If the result is abnormal, then the male partner is tested. If both are carriers and prenatal testing showed the fetus is affected, the parents can decide whether or not to terminate the pregnancy. For screening to be effective, it needs to be carried out prior to pregnancy or at the early stages of pregnancy, since termination of pregnancy for affected fetuses may not be acceptable to some quarters on ethical/religious grounds.

Thalassaemias are common in the Mediterranean area. At present, these countries have the best models of Thalassaemia control programmes, which have been proven to be effective, acceptable and cost-beneficial. These programmes embody the WHO principles of a control programme for a hereditary disorder, i.e. “a comprehensive strategy combining the best possible patient care, with prevention by community information, carrier screening and counseling and the offer of prenatal diagnosis”.

The successful development of an effective programme depends on the recognition of the health authorities and expert centres that haemoglobin disorders are a public health problem, and that appropriate strategies, local epidemiology, current services and available resources need to be taken into account.

Based on the annual sales of Desferrioxamine for iron chelation therapy in beta Thalassaemia major cases, less than 20% of patients are on chelation therapy, with the remaining 80% destined to die from complications of iron overload. While this estimate is based on the use of single vials daily, patients over the age of 10 years need 2 vials daily, which may further lower these figures.

The management of Thalassaemia cannot be confined to only treating thalassaemics, as the new cases continue to drain resources, treatment of this disease being costly. Thus, there is a need for a screening programme.

4.2 Treatment

The mainstay of treatment of Thalassaemia is blood transfusion combined with iron chelation therapy. While blood transfusion has the advantage of prolonging the patient’s life, it causes iron over-load, which subsequently damages the vital organs. Iron over-load is also due to increased gut absorption. The transfusion regime for Thalassaemia major aims to suppress erythropoiesis sufficiently, to allow optimal growth and activity, and minimize the iron load.

4.2.1 Blood transfusion

Regular blood transfusion remains the main conventional treatment modality for Thalassaemia major. Before the advent of transfusion treatments in the 1960s, patients died of severe anaemia at a very early age. Patients who are poorly transfused have poor survival and high morbidity, as shown by a study in Papua New Guinea, where patients who were symptomatically anaemic, and receiving transfusion with no chelation or splenectomy, developed hypersplenism by the age of 3-4 years and usually died before they were than 9 years of age (Smiley, 1986).

In Malaysia, it is estimated that there are about 2 400 transfusion dependent Thalassaemia patients who receive regular packed cell transfusions 3-4 weekly to alleviate the chronic anemia that is associated with the disease. However, the exact number is not known due to the lack of a patient registry currently. It is estimated that 75 % of transfusion dependent patients use blood filters and

less than 30% are receiving iron chelation, possibly since patients need to pay for Desferrioxamine (unpublished data). Hence, with frequent blood transfusions, most patients face problems of transfusion related infections and alloimmunisation to transfused red cells, as well as complications of iron overload to vital organs like heart, liver, pancreas and pituitary gland.

The following are the options for blood used for transfusion and various recommended regimes:
Neocytes
Neocytes are young red cells, which are harvested from normal donors. In theory, these red blood cells can prolong patients' life span and they subsequently need less frequent transfusion.

Leukocyte reduced packed RBC
These are packed red cells with the the level of leukocytes reduced to less than 5×10^6.

Supertransfusion regime
Under this regime, the pre-transfusion Hb is kept above 12g/L

Hypertransfusion regime
The pre-transfusion Hb in this regime is usually above 10-12 g/L

Moderate transfusion regime
In the moderate transfusion regime, the pre-transfusion Hb is maintained between 9-10g/L.

4. 2.2 Chelation therapy
The management of severe forms of ß Thalassaemia entails regular blood transfusion with chelation therapy to prevent the effects of iron accumulation. Iron removal in transfusional iron overload is achieved using chelation therapy with chelating drugs like Desferrioxamine (DF) and Deferiprone (L1). Effective chelation therapy in chronically transfused patients is achieved when iron chelators remove sufficient amounts of iron, equivalent to that accumulated in the body from transfusion, to be able to maintain the body iron load at a non- toxic level. For this, chelating drugs have to be administered daily in high doses.

Desferrioxamine Mesylate was first introduced in short-term studies in iron-loaded patients in the early 1960s. However, it is estimated that less than 10% of patients requiring iron chelation therapy worldwide are able to receive Desferrioxamine, because of its high cost, low compliance of patients, and toxicity in some cases. It has gained acceptance as standard therapy in those countries able to support the high costs involved, and has been a life-saving drug for thousands of patients in the last 40 years. Desferrioxamine is mostly administered by subcutaneous infusion (40-60 mg/kg, over 8-12 h, 5 days per week). It is effective in iron removal and has low toxicity. Children treated in this way, and who are able to comply with overnight infusions of Desferrioxamine together with a low dose of vitamin C, grow normally and do not succumb to the life threatening complications of iron overload. In addition to extended survival free of iron-induced complications, it has dramatically improved the quality of life in well-chelated patients. Indeed, iron-chelating therapy for Thalassaemia major has resulted in one of the most dramatic alterations in morbidity and mortality associated with a genetic disease.

In the last 10 years another orally active iron-chelating agent, Deferiprone (1, 2 dimethyl-3-hydroxypyrid-4-one, L1) has emerged that has been said to have the potential to change the prognosis of all transfusional iron-loaded patients. It has been studied extensively in clinical trials.

4.2.3. Haemopoitic stem cell transplantation

Haemopoitic stem cell transplantation is the conventional curative option for Thalassaemia patients. This therapy infuses the Thalassaemic patients with stem cells harvested from a compatible donor. If engraftment occurs, these normal stem cells will then re-populate the recipient's marrow and proliferate to produce normal red blood cells. If the treatment is successful, the patient is no longer transfusion dependent. The sources of stem cells include bone marrow (compatible sibling or matched unrelated donor), cord blood (sibling or cord blood registry) and peripheral blood (sibling or unrelated donor). As families with Thalassaemia tend to have less children, the chances of obtaining a normal and compatible sibling donor is about 15-25%. However, stem cell transplantation is recommended for patients with compatible sibling donors.

Bone marrow transplant (BMT) offers the potential of a permanent cure if a sibling is found to be a HLA compatible donor. The standard conditioning regimen for marrow transplantation in hemoglobinopathies is Buslphan/Cyclophosphamide with or without antithymocyte globulin. Certain experimental groups include total body irradiation as part of their conditioning regimen (Mentzer, 2000)

4. 2.4. Other treatment modalities

(i) Augmentation of Fetal Hemoglobin Synthesis

The molecular mechanisms involving the persistence of fetal hemoglobin in the first year of life are not completely understood. Inducing the production of HbF again in patients with Thalassaemia offers the prospect of a better quality of life without the need for blood transfusions. The drugs used for this are Hydroxyurea, 5-Azacytidine etc., which inhibit the proliferation of cells, having the same effects as those used in cancer treatment.

(a) Hydroxyurea

Hydroxyurea is a potent ribonucleotide reductase inhibitor that is capable of inducing hemoglobin F (HbF) synthesis. It has been used for a number of years in the treatment of various myeloproliferative disorders. It has been widely investigated, and has been shown to increase fetal Hb in patients with sickle cell disease. It is believed that Hydroxyurea replaces the poorly hemoglobinised, readily sickling and short-lived erythroid cell population with a new cohort of precursors with an active Hb F synthesis.

(b) 5 Azacytidine

5 Azacytidine (5-AzaC) is an S-phase specific agent used as a chemotherapeutic agent for the treatment of acute myeloid leukemia. It has been shown to stimulate Hb F production in animal studies.

(c) Butyrates

Butyrates have been shown to modify Hb F production in some patients. This was following the original observation that the infants of diabetic mothers, who often have raised blood levels of α amino butyric acid, have delayed switching from fetal to adult hemoglobin production. The mode of action may involve interaction with hyperacetylation sites in DNA with an enhancing effect on the γ promoter.

(d) Erythropoietin

This has also been used in the treatment of Thalassemia, but its high cost constraints its use on a larger scale.

(e) Combination Agents
A combination of Sodium butyrate and Hydroxyurea has been used in some patients.

(ii) Gene Therapy
Gene therapy remains an attractive option for patients in whom treatment with bone marrow transplantation is not possible. However, there are still many obstacles to be overcome. The correction of genetic deficit of the hematopoietic system needs the transfer of genes into stem cells, for which there has been some progress in the development of transduction methods and vectors. Other problems include the identification of all sequences needed for stable, high level expression of the genes and the development of more effective and safe vectors for the transfer of genes. Unless significant medical breakthroughs occur, gene therapy for Thalassaemia may not be possible in the near future.

(iii) Others
Nutrition, vitamin support and psychology therapy are other modalities used in the treatment of Thalassaemia patients. Vitamin C is only given to those with established depletion and those who are on chelation therapy.

As all Thalassaemic children have a normal immune defense system, they undergo the normal immunisation schedule. For Thalassaemic children requiring splenectomy, additional immunization with Haemophilus influenza B, pneumococcal and meningococcal vaccines is usually carried out.

5. METHODOLOGY
Details of the methodology are as indicated in Appendix 1

6 RESULTS & DISCUSSION

6.1 Screening and Prevention of Thalassaemia
In Cyprus, there were 597 known homozygotes alive in 1980, and of these 77% were receiving regular chelation therapy. It was also found that 44.7% of the total output of the blood bank in Nicosia was used for Thalassaemics in 1978. The total cost of Desferrioxamine alone represented 6% of the annual budget of Ministry of Health in 1979. Based on these figures, it is estimated that the cost of prevention annually (including antenatal diagnosis), represents the expenditure for the treatment of patients for 5 weeks (Angastiniotis, 1986).

In Cyprus, a Thalassemia management programme was developed in the following sequence:
1. Improving curative services with adoption of a common management protocol.
2. Provision of adequate, safe blood with campaigns to increase public awareness
3. Provision of obstetric and laboratory facilities for prenatal diagnosis
4. Setting up population screening and counseling programmes
5. Community involvement, public information and education

6. Evaluation of programme (Angastinoitis, 1981).

6.1.1 Effectiveness

A successful screening program for Thalassaemia was performed in Cyprus, where all couples who were getting married were asked to provide certificates showing their alleles. There were only 18 homozygous beta Thalassaemia births in 1979, compared to 77 that were expected, mainly due to availability of antenatal diagnosis from 1977 (Angastinoitis, 1981).

Thalassaemia is a major health problem in Thailand, and despite a prevention programme there has been no decrease in the prevalence of the disease, due to a lack of awareness, implying that genetic counseling was a failure. This failure has been attributed to a lack of recognition of problems related to Thalassaemia, unorganized teamwork and services, lack of knowledge and inadequate numbers of counselors, lack of Thalassaemia support groups, and inadequate research in Thalassaemia prevention and control (Dhamchareeet al., 2001).

In Singapore, the incidence of new cases of Beta Thalassaemia major has decreased dramatically ever since it advocated population screening from 1980, and antenatal screening from 1990, with only 3 new cases in the last 5 years. The strategy employed was cascade screening (i.e. screening spouses and relatives) along with antenatal diagnosis, resulting in a high pick up rate among this high risk sub-population. A national Thalassaemia registry was set up in 1992 (Ng et al, 2002).

In Sardinia, in mid-1990, the carrier-screening program detected 30,500 carriers and 1,544 couples at risk, as well as another 812 couples known to be at risk because of an affected child. Thus, 87 % of the couples at risk knew their status. Approximately 90% of potential cases are prevented by the use of prenatal diagnosis and selective abortion. Although the population of Sardinia is mainly Catholic, less than 1% of the couples with an affected fetus decided not to have an abortion. Despite this, residual cases of Thalassaemia occur due to parents' ignorance of Thalassaemia (67%), mispaternity (13%), and rejection of abortion (20%). This shows the usefulness of an effective carrier screening, prenatal screening, and counseling service (Cao, 1991).

Palestine has a beta Thalassaemia carrier rate of 3-4%, with about 20-25 new cases annually, and about 420 patients receiving treatment. In addition, there are families with 5 affected children. Even though Desferrioxamine is available for treatment, 50% of patients have iron overload due to poor compliance as well as consanguineous marriages (77%). Since May 2000, premarital testing for Thalassaemia has become mandatory by law, while in 2001, screening of 7th grade students for Thalassaemia has been implemented (Younis, 2002).

Bahrain implemented a national program on screening and education of the public in 1997.In addition, premarital counseling prior to marriage is mandatory. These resulted in a 60% decline in the incidence of sickle cell disease in 2000 with less than 1% babies suffering from sickle cell disease (Al-Arrayed, 2001).

Iran has also implemented a successful Thalassaemia prevention program through its primary health care system since 1991, offering termination of pregnancy for affected fetuses in the first 100 days of pregnancy.

In Lebanon, it was shown that the majority of couples (59%) were definitely in favour of prenatal diagnosis, 23% were uncertain and 18% were opposed to it (Zahed, 1997).

6.1.2 Target population for screening

(i) School students

A study involving 1650 secondary students aged 16-18 years identified 4.3% of them to be Thalassaemia carriers (Sirdah et al, 1998). Studies in Canada demonstrated that the screening for Thalassaemia in students of Jewish and of Mediterranean origin above the age of 16 years has been successful over 20 years without any apparent psychological or social harm (Mitchell, 1996). The screening of high risk groups in high school enabled carriers who were ignorant of their genetic status, to make informed decisions about having children, and consequently, Thalassaemia major has declined substantially in Montreal (Mitchell et al., 1996). In Hong Kong, a similar study where high school students aged 14-19 years were screened, found that 75% of the eligible students received parental consent to be tested, and 3.4% were found to have beta Thalassaemia. There were no details of psychological reactions of students who were carriers as well as information on follow-up studies (Lau, 1997). However, although screening of high school students is logistically more realistic than the screening of young adults, it has been suggested that on ethical grounds, genetic testing without immediate medical benefits should never be done in adolescents. In the Montreal study, the community was consulted during the planning stages for screening, and confidentiality was stressed, while in the Hong Kong study only the principals and teachers were consulted. Another study assessing the impact of a screening program among high school children in France, found that despite the time lapse between screening, information and pregnancy (mean of 15 years), the information was well conserved, and resulted in testing of the partner. Thus, the screening program was effective in motivating requests for prenatal diagnosis (Lena-Russoet al., 2002).

(ii) Premarital screening programme

Pre-marital screening or screening before marriage for Thalassaemia can prevent the birth of beta Thalassaemia major. However, Iran has a large population of Thalassaemics, due to restrictions on abortion previously, and thus, the routine prevention of thalassaemic births was not possible by this means. Subsequently, a study found that 90% of the couples that tested positive decided not to marry, and thus no new cases of beta Thalassaemia major were detected (Ghanei et al., 1997).

(iii) Inductive or cascade screening programme

Inductive screening or “cascade screening” refers to the heterozygotes testing of relatives of known carriers of Thalassaemia. In Singapore, inductive screening together with the implementation of population screening and antenatal screening has resulted in high pick up rates and identifying couples at risk, with no new cases detected in 2002 (Ng et al., 2002). A study in India also showed good evidence of the feasibility of Thalassaemia control by extended family screening (Saxena et al., 2002)

6.1.3 Cost effectiveness - Thalassaemia prevention programme

Cost benefit analyses in the United Kingdom, Sardinia, Greece and Canada have shown that the cost of a nationwide Thalassaemia prevention program based on prenatal diagnosis are trivial compared with the benefits of reducing treatment costs (Ostrowsky, 1985). A similar cost benefit analyses of a combined educational and national prenatal screening program for Thalassaemia in Israel showed benefit cost ratios of 4.22 to health services and 6.01 to society (Ginsberg et al 1998). In the United Kingdom, the estimated lifetime cost for comprehensive treatment of beta Thalassaemia major ranges from £ 188,000 to £226,000 (Karnonet al., 1999).

6.1.4 Laboratory tests for Thalasseamia screening

The British Committee for standards in Haematology recommends MCH as the parameter for screening as the first step where a value of <27 pg* indicates the need to quantity Hb subtypes (BSH, 1998). A local study in Malaysia also found MCH and the automated HPLC approach to quantify HbA2 as being an appropriate approach for screening and identification of classical beta Thalasseamia trait carriers (George, 2001). Osmotic fragility test (OFT) is sensitive and cost effective for detection of beta Thalassaemia trait. Carrying out OFT with 0.37% buffered saline solution is inexpensive, and accurate enough to be used as a single screening test in areas with limited laboratory facilities and economic resources (Maram, 2000).

6.1.5 Ethical, legal and social issues in genetic screening

Ethical issues

Ethical aspects of management of β-thalassaemia, falls back to the traditional sources of ethical guidelines in medicine. These ethical principles include beneficence: giving highest priority to the welfare of persons and maximizing benefits to their health; non-maleficence: avoiding and preventing harm to persons or, at least, minimizing harm; respect for the autonomy of persons: respecting the self-determination of individuals and protecting those with diminished autonomy and distributive justice: treating persons with fairness and equity, and distributing the benefits and burdens of health care as fairly as possible in society (Narimah, 2000).

In medical genetics the main concerns, are that genetic information may affect an entire family, rather than only the individual; genetic discoveries may be predictive of future adverse events in an individual's or family member's health, and that the choices of the present may affect future generations.

There are concerns about the need for informed consent and about the availability of genetic counselling and support prior to and after screening (Chadwick et al., 1998).

It is the moral dilemma about termination of pregnancy that often causes controversy in prenatal diagnosis. Prenatal diagnosis may be considered controversial because the results may be used to justify termination of pregnancy, which may be a controversial issue to a section of today's society. Those who oppose it consider it to be contrary to the goal of medicine, which is to save lives. Those who support medical termination of pregnancy do so because they wish to prevent unsafe abortions, reduce suffering and poor quality of life for children whom are severely affected by their respective genetic conditions (Chadwick et al., 1998). It has been suggested that physicians opposed to abortion on moral grounds and therefore under difficulties in counseling their patients about screening, have an ethical obligation to refer their pregnant patients to a colleague.

Legal issues

All genetic testing must be performed by accredited medical laboratories and staffed by scientists and technologists experienced in genetic technology (Chadwick et al, 1998).

With respect to termination of pregnancy, in 1989, Malaysia amended the penal code to permit abortion within 120 days of conception if the continued pregnancy poses a threat to the woman's life or to her physical or mental health greater than would the termination of the pregnancy (The Penal Code (Amendment) Act 1989 (Act A727)).

Social issues

There are human risks involved in all genetic screening programs and these include labeling, discrimination, loss of self-esteem, prevention or damage to parent-child bonding, stigmatization, unnecessary anxieties and invasion of privacy. Hence, a proper centrally planned genetic screening programme with its various institutional ethical safeguards is crucial and desirable. The alternative is an unregulated genetic screening tests being offered by commercial concerns to anxious families and couples without appropriate supervision (Chadwick et al, 1998). A study in India of 200 families with Thalassaemia found that ignorance and prejudice in the community led to social isolation for families (Sangani et al., 1990).

Considering the long-term effects of prenatal diagnosis on couples at high genetic risk of thalassaemia, a study of 102 couples with 356 pregnancies of which 302 were viable, found that 88% achieved a family unburdened by thalassaemia. Since each couple at-risk (where both partners have β-thalassaemia trait) has a 1 in 4 risk of having an affected fetus in each pregnancy, this finding is a significant positive development (Petrou & Ward 2000).

With respect to the role of religion pertaining to the termination of pregnancy, in Pakistan, Islamic scholars have ruled that a pregnancy can be terminated before 120 days of gestation if a severe disorder is confirmed in the fetus (Ahmad et al., 2000). In July 2002, the Department of Islamic Development (Jabatan Kemajuan Islam Malaysia -JAKIM) and the National Fatwa Council Malaysia reportedly also took a similar stand (New Straits Times 17th Oct 2002).

Genetic Counselling

There is a need to have a control program adapted to particular populations, with proper information and counseling, and appropriate financial resources to make it a success (Zahed, et al, 1997). In Pakistan, a study done after a year of introduction of screening service showed that, although 72% were aware of the availability of a screening test, only 56% went for a second prenatal diagnosis. The reasons were cost of the test, fear of undergoing test and lack of a clear explanation (Ahmad et al, 2000). This is not unusual for families with inherited disorders once they have come to terms with the various genetic conditions.

Genetic counselling is the process of providing information to at-risk couple and families about a genetic condition, in particular information about the diagnosis, recurrence risk, burden of disorder and the various reproductive option, together with helping the families coming to terms with the issues in a non-directive manner. A study found that after confirmation and proper counseling, 88.7% of women with affected fetuses opted for termination of their pregnancy, while the rest declined principally on religious grounds. Religious objections have frequently been cited as a reason for not having comprehensive genetic screening programmes (Ahmed S et al, 2000).

CONCLUSION

There is sufficient evidence that a screening and prevention programme is effective for the control of β-thalassaemia trait.

6.2 Complications of Thalasssemia

6.2.1 Hepatitis C, hepatitis B and HIV

Prevalence studies found that the common infections occurring in Thalassaemic patients are Hepatitis C (2.2 – 44%) followed by Hepatitis B (1.2 – 7.4 %) and HIV (0-9%) (Al-Sheyyab et al., 2001; Moatter et al., 1999; Sur et al., 1998; Laosombat et al., 1997; el-Nanaway et al., 1995; Kumar et al., 1994; Sen et al., 1993; Isahak et al., 1993; Costaglia et al., 1992; de Montalembert, 1992; Mozzi et al., 1992; William et al., 1992). A local study at Hospital University Kebangsaan Malaysia showed a seroprevalence rate of 22.4% and 1.2% for Hepatitis C and Hepatitis B respectively in Thalsassemia patients being treated (Jamal et al., 1998).

6.2.2 Cardiac complications

Most of the cardiac complications found in Thalassaemia patients were heart failure (5.4-12%) (Kremastinos et al., 2001; Aessopos et al., 2001; Fucharoen et al., 2000; Borgna-Pignatti, 1998; Kremastinis et al., 1995; Favilli et al., 1993; Kremastinis et al., 1984), heart disease/cardiac impairment (37-51%) (Sau et al., 1995; Richardson et al., 1993; Wolfe et al., 1985), arrhythmias (5%) (Borgna-Pignatti, 1998), left ventricular ejection fraction (<45% -13-37%) (Aldouri et al., 1990; Kremastinos et al., 1995; Hahalis et al., 2001; Halilis & Monalis., 2002;), pulmonary hypertension (59.1%) (Aessopos et al., 2001) and diastolic dysfunction (50-54%) (Vaccari et al., 2002; Yaprak et al., 1998;Hou et al., 1994). There is a significant correlation between serum ferritin levels and myocardial iron grade and content (Lombardo et al., 1995). A study found a higher incidence of heart problems in those with poor iron chelation compliance (Wolfe et al., 1985). Another study found that the risk factors of heart disease includes old age, late age of commencement of Desferrioxamine, higher liver iron and higher serum ferritin levels (Richardson et al., 1993). Cardiovascular T2-star (T2*) magnetic resonance is useful in detecting early myocardial overload (Anderson et al., 2001). It was found that mean survival of those not on chelation was 17.4 years versus 31 years for those who received hypertransfusion and chelation (Ehlers et al., 1991). Another study states that survival after a heart failure episode was 48% (Kremastinos et al., 2001).

6.2.3 Short stature in patients with Thalassaemia

The prevalence of short stature reported ranged from 8-75%, these variations being due to heterogenous patients, quality of treatment and variation in compliance to iron chelation therapy from one institution to another (Soliman et al., 1999; Low et al., 1998; Theodoridis et al., 1998; Caruso-Nicoletti, 1998; Roth et al., 1997; Kwan et al., 1995;Grundy et al., 1994). A local study by Hospital University Kebangsaan Malaysia found a prevalence of short stature of 54.5% for transfusion dependent Thalassaemics (Hamidah et al., 2001). Truncal shortening was also seen in the majority of patients with short stature (Rodda et al., 1995; Hamidah et al., 2001). There was also a high prevalence of defective growth hormone secretion in Thalassaemic children (Soliman et al., 1999), and this has been said to be related to neurosecretory dysfunction due to iron overload rather than liver damage (Roth et al., 1997).

Recombinant growth hormone therapy has been found to have a role in the treatment of short stature in Thalassaemics (Cavallo et al., 2001; Theodoridis et al., 1998).There seems to be significant differences in the growth velocity of patients with short stature who were treated with growth hormone compared to those who did not receive therapy (Arcasoy et al., 1999). Intensive chelation therapy has been found to have a positive effect on linear growth (Gracia- Mayor et al., 1993). Another study in Thailand also found that adequate iron chelation and hormonal treatment enabled patients to achieve normal adult height (Viprakasit et al., 2001).

6.2.4 Pubertal delay in patients with Thalassaemia

There is a high prevalence rate of pubertal delay, ranging from 38-90% in both sexes (Filosa et al., 2001; Soliman et al., 1999; Saka et al., 1995; Kwan et al., 1995; Yesilipek et al., 1993; Borgna-Pignatti et al., 1985). A local study found that 24% of thalassaemics had delayed puberty (Jamal et al, unpublished data). The development of secondary sexual characteristics in thalassaemic children was found to be markedly delayed compared to their non-thalassaemic siblings (George et al., 1997). It was also found that there is 74% primary amenorrhoea (Soliman et al., 1999).

Hypogonadotrophic hypogonadism has been found to be the main cause of delayed/failed puberty (Soliman et al., 2000). It was also found that Thalassaemics have decreased gonadotrophin reserves and showed normal gonad response to human menopausal gonadotrophin (De Sanctis et al., 1998). Iron overloaded Thalassaemics with failed puberty also had abnormal GnRh-GTH secretory dynamics (Chatterjee et al., 2001). However, the prepubertal pattern of GHRH response was restored in patients receiving testosterone (Leheup et al., 1991). Those with severe iron overload and organ damage were found likely to have irreversible damage to their hypothalamo-pituitary axis whilst those with less severe overload were likely to have potentially reversible hypogonadotrophic hypogonadism (Chatterjee et al., 2000). Thus, starting chelation therapy before pubertal age can help patients attain normal sexual maturation (Bonspiegel-Weintrob et al., 1990).

6*.2.5 Diabetes Mellitus in patients with Thalassaemia*

The prevalence of diabetes range from 5.4-19.5% (Chern et al., 2001; Gulati et al., 2000; Borgna-Pignatti et al., 1998; el-Hazmi, 1994), whilst impaired glucose tolerance is seen in 7.9-86% (Chern et al., 2001; Gulati et al., 2000; Zuppinger et al., 1979). It was found that most complications could be avoided if serum ferritin levels were less than1500μg/L (Telfer et al., 2000). The frequency of diabetes in adult patients has been seen to be significantly increased by HCV infection (Labropoulou-Karatza et al., 2000).

6.2.6 Osteoporosis in Thalassaemia patients

The prevalence of osteopenia/osteoporosis amongst patients with Thalassaemia ranged from 39-67% (Chan et al., 2002; Bielinski et al., 2001; Jensen et al., 1998; Katz et al., 1994; Giuzio et al., 1991). A local study found a prevalence of osteoporosis of 84% in transfusion dependent Thalassaemics (Jamal et al, unpublished data). Lumbar level osteoporosis is observed in treated Thalassaemic patients whilst it involves both the lumbar and femoral neck regions in those who are untreated (Lasco et al., 2001). The skeletal changes seen in thalassaemics include lower limb length discrepancy (16.6%), upper limb-length discrepancy (5.5%), axial deviation of the limbs (8.3%) and osteochondrosis (2.7%) (Giuzio et al.,1991). Thalassaemia patients have been found to have less than 30% spinal bone mineral density (Anapliotou et al., 1995; Soliman et al., 1998; Molycda-Athanasopoulou et al., 1999).

Calcitonin therapy with calcium has been found to improve both bone pain as well as the radiological signs of osteoporosis (Canatan et al., 1995). Here too, it was found that hypogonadism seems to play an important role in the development of osteopenia-osteoporosis, since continuous hormone replacement therapy with estrogen for females and hCG for males has been found to improve the bone density parameters (Anapliotou et al., 1995)

6.3 Treatment

6.3.1 Blood transfusion

(i) Type of Blood Products.

(a) Leukocyte Reduced Red Cells

Transfusion reaction has been found to be reduced with the use of leukocyte reduced red cells (Ohene-Frempong et al., 1987), while filtered blood was shown to be as effective as frozen blood in eliminating non-haemolytic febrile transfusion reaction (Marcus et al., 1985). Transfusion reactions were found to occur in about 1.1% of transfusions when 90% of the blood was leukocyte poor (Rubella, 1990).

The use of a leukocyte removal filter (Sepacell R-500) resulted in a reduction of the patient reaction rate from 63% to 3.7%, and the transfusion reaction rate from 13% to 0.5%, compared with standard packed red cells (PRC) or buffy-coat-depleted PRC (Sirchia et al 1987;Tan et al., 1993). However, febrile reaction was not significantly reduced (Tan et al., 1993).

While leukocyte reduction can be carried out in the blood bank (pre-storage filtration) or with a bedside filter, U. Sprongoe-Jakobsen et al., (1995) showed that bedside filters are not as efficient as blood bank filter systems, since there is a 13% failure rate. However the Red Blood Cell (RBC) loss is significantly higher with blood bank filter systems, while the timed workload for both systems did not differ significantly. The frequency of reactions to filtered blood were found to vary significantly according to the type of filter used - Erypur (0.7%), Imugard (2.7%), Leucostop (0.7%), Miropore (2.1%), and Sepacell (0.6%) (Reverberi, & Menini, 1990). A similar finding was obtained with other filters - Microaggregate Filtered Red Cells (7%), Buffy Coat Poor Red Cells (0.3%), Washed Buffy Coat Poor Red Cells (0.1%), Cotton Wool Filtered red cells (1%) and Frozen Red Cells (0.2%). This correlated well with the degree of leukocyte depletion (James et al., 1986).

There is sufficient evidence to conclude that leukocyte reduced red cells are effective in reducing transfusions reactions, the better the filter, the greater the reduction in transfusion reactions. The filtration can be done either in the blood bank before storage, or at the bed -side before transfusion.

(b) Neocytes

The use of neocytes has been found to lengthen the transfusion interval from 30 ± 2.5 days to 43 ± 4.5 days was (Propper et al., 1980). With neocyte transfusion it was also found that less blood was required to maintain the pre-transfusion Hb at 9.0g/dL (Cohen et al., 1984). The red cell requirement was also found to be reduced by 18%- 22 %(kg/year) during the neocyte period (Kevy et al., 1988; Bertholey, 1990). A reduction of blood load by 20.2 ± 9.1% resulted in a reduction of blood requirement by 10% to 34% (Spanos, 1996), so that there were6.9% to 14% fewer transfusions (Kevy, 1991; 1988). However, a prospective randomized controlled trial showed that there was no difference seen between neocytes and whole blood use with respect to transfusion interval, mean Hb and rate of Hb fall (Marcus, 1985).

There is sufficient evidence to conclude that use of neocytes for transfusion can decrease blood requirement.

(ii) Transfusion regimes

(a) Pretransfusion Haemoglobin (Hb) Level.

It was recommended that the Hb level in Thalassaemia patients need to be maintained at least above 8 g/dL for normal growth (Kattamis et al 1970). Others found that pre-transfusion Hb levels of 9-10 g/dL are sufficient (Cazzola et al., 1997 ; Prati et al., 2000). However, in the 1980s super-transfusion (pre-transfusion Hb above 12 g/dL) was advocated. These caused an increase in blood requirement but subsequently there was a return to standard regime requirement after a few months (Hb > 10g/dL) (Propper et al., 1980; Masera et al., 1982). Hyper-transfusion baseline Hb of 10 -12 g/dL was also practiced for many years (Cazzola et al., 1997, Albo et al., 1995; Piomelli, & Leow, 1991). However, a review noted that the clinical value of super-transfusion has not yet been clearly established, since initial reports found that a higher baseline Hb could be maintained without increased transfusion requirement (Ohene-Frempong et al., 1987).

It has been found that Beta Thalassaemia trait patients had an erythroid activity of 1-3 times normal, while transfusion dependent beta Thalassaemia Major patients with a pre-transfusion Hb of 10-11 g/dL had erythroid activity of up to twice the normal rate. On the other hand, those with a pre-transfusion Hb of 9-10 g/dL had up to 4 times the normal rate, while in patients with a pre-transfusion Hb of 8.6-9g/dL the rate was 2-6 times the normal rate. Hence, it was concluded that a pre-transfusion Hb of ≤ 9 is not advisable, and that keeping pre-transfusion Hb to 9-10 g/dL may be sufficient to provide suppression of erythropoiesis and allow a reduction in blood consumption, compared to classical hyper or super-transfusion (Cazzola et al., 1995). This finding was support by a prospective trial during the period of moderate transfusion regimen, where transfusion requirements decreased from 137± 26 to 104 ± 23 mL per kg per year of red cells, the saving in transfusion iron averaging 40 mg/kg/year per patient. The mean serum ferritin also decreased from 2448±1515 to 1187±816 μgm/l with half of the patients achieving serum ferritin levels lower than 1000 μgm/l. The proportion of patients having spontaneous puberty development increased significantly, and the erythroid marrow activity did not exceed 2-3 times normal levels in most study subjects, being lower than the erythroid marrow activity in the Thalassaemia intermedia control group (Cazzola et al., 1997).

However, it has been noted that even with proper chelation, some patients continue to suffer from transfusion iron overload and its complications (Cazzola et al., 1997; Albo et al., 1995). A retrospective study found that growth was not significantly better in the group where transfusion was started at low Hb level (8.5g/dL) with chelation during adolescence, as compared to the group with transfusion at high Hb level (10-10.5g/dL) and chelation during childhood or at the age of 2 years (de Sanctis et al., 1994).

(b) Transfusion interval

The difference in transfusion interval of 2 – 4 weeks has no measurable effect on blood requirements (Rubella, 1991). However 50% more blood is required to transfuse every 6 weeks than every 3 weeks (Piomelli, 1991).

(iii) Compatibility testing

The development of red cell antibodies (alloimmunisation) is a known and common complication of chronic transfusion therapy, its frequency ranging from 3% to 23.5% (Singer et.al., 2000; Hmida et al., 1994; Spanos et al., 1990; Fonsatitkul et al., 1988; Tardtong et al., 1988; Michail-Merianou et al., 1987). New antibodies include Anti-E, anti-C and anti-Kell groups.

Alloimmunisation was found to involve the Rh system and the Kell system (Hmida et al., 1994, Spanos et al., 1990), and it was found to be significantly lower in patients in whom blood transfusion was started before the age of 3 (Spanos et al., 1990). Patients who received blood matched for ABO, Rhesus (CDE) and Kell antigen system were found not to develop alloimmunisation (Hmida et al., 1994, (Singer et al., 2000). A study in California, USA found that alloimmunisation was higher in patients who have had splenectomy, and that erythrocyte auto-antibodies (positive Coombs test) were developed resulting in severe hemolytic anemia. However, in one study there was no difference in the overall frequency of alloimmunization between the group receiving ABO and Rh(D) compatible blood and those receiving CcEeK antigen compatibility as well, but there was a statistically significant difference between the children who had transfusions started early as compared to those who were started later in life, irrespective of the transfusion policy (Michail-Merianou et al, 1987).

It can be concluded that there is sufficient evidence that leukocyte reduced red cells are effective in reducing transfusion reactions, the better the filter, the greater the reduction in transfusion reactions. The filtration can be done either in the blood bank before storage or at the bedside before transfusion. There is evidence that use of neocytes for transfusion can decrease blood requirement. There is sufficient evidence to conclude that the pretransfusion Hb level should be not less than 9g/dL and more than 10 g/dL, so as to ensure adequate suppression of erythropoiesis (and its complications) while reducing blood consumption and iron loading, and thus ensuring a better quality of life, the transfusion interval ranging from 2-4 weeks.

There is evidence that group and cross matching for ABO, Rh (CDE) and Kell antigen will reduce the incidence of red cell alloimmunisation to a very low level compared to only routine ABO and RH (D) screening, and this is especially so with patients who start transfusion much later in life (> 3 years old).

(iv) Cost

The cost of producing comparable amounts of red cells has been found to be $134.80 for neocytes compared to $61.70 for normal frozen blood (Cohen et al., 1984).

6.3.2 Chelation Therapy

(i) Safety

The most common adverse effects associated with Desferrioxamine include ocular and auditory abnormalities, sensory-motor neuro-toxicity; changes in renal function, and pulmonary toxicity (Davies et al., 1983; Orton et al., 1985; Koren et al., 1989; Porte et al., 1989; Freedman et al., 1990)

Bone dysplasia was seen in Thalassaemia patients who begun chelation with Desferrioxamine before the age of 3 years, but it could not be determined whether the dysplastic bone growth was related to dosage of the drug or to the age of onset of chelation (Brill et al., 1991). Radiological abnormalities of the long bones have also been observed, but while the exact cause is uncertain, probably Desferioxamine had a role in these toxic effects (Orzincolo et al., 1992). It was also found that Desforioxamine induced spinal deformities (Hartkamp et al., 1993).

Most Desferrioxamine toxic effects have been observed in patients with administration of doses exceeding 50 mg/ kgbody weight, or smaller doses in the presence of very modestly elevated body iron burdens. The toxicity of Desferrioxamine appears to be enhanced as the serum ferritin concentration declines, and Desferrioxamine dose increases.

Desferrioxamine -induced toxicity can be avoided by regular, direct assessment of body iron burden with regular evaluation of the hepatic iron concentration. If hepatic iron concentration is not regularly assessed, a "toxicity" index, (daily dose of Desferrioxamine (mg/kg) divided by the serum ferritin concentration [µg/L]) should be calculated for each patient every 6 months, and this should not exceed 0.025.

(ii) Effectiveness

The Impact of Iron-Chelating Therapy on Cardiac Disease and Survival

The beneficial effects of Desferrioxamine therapy on survival and cardiac disease in patients with Thalassaemia were first reported in the early 1980s, where a study in Britain, found that patients who had received average weekly Desferrioxamine doses of more than 4gm over a few years were less likely to die in the near future than patients of similar ages who had received less or no Desferrioxamine (Modell et al., 1982). Freeman et al., (1983) using radionuclide angiography to assess the incidence of sub-clinical abnormalities of left ventricular function showed normal exercise response in patients with chelation therapy. It was also found that Desferrioxamine had a role in preventing cardiac disease (Wolfe et al., 1985). Another study also showed a significant overall improvement in left ventricular function with a significant drop in serum ferritin (Aldouri et al., 1990).

Olivieri et al., (1994) identified factors relating to the age at which chelation therapy was started, of and the serum ferritin concentration before chelation therapy was given as affecting cardiac disease survival. It was found that patients with less than 33 % of the serum ferritin values exceeding 2500 mg/ml had 100 survival rates without cardiac disease after 10 years of chelation therapy, and 91 % survival after 15 years. Brittenham et al., (1995) showed that early use of proportional amount of Desferrioxamine on transfusional iron load, reduces the body iron burden and helps protect against diabetes mellitus, cardiac disease, and early death in patients with Thalassaemia major.

The impact of iron-chelating therapy in liver disease

Subcutaneous Desferrioxamine has been found to have beneficial effects on iron loading within the liver by reducing iron concentration in the liver, improvement in liver function and arrest of hepatic fibrosis (Cohen et al., 1981).

Impact of iron-chelating therapy on endocrine function and growth

The effectiveness of Desferrioxamine in the prevention of growth failure and gonadal dysfunction was first reported in a cohort of patients regularly treated since mid-childhood, 90% of whom reached normal puberty. In contrast, in a group of patients in their early teens who were administered a relatively lower dose of Desferrioxamine, only 38% achieved normal pubertal status. Olivieri et al., (1992) reported abnormal linear growth and metaphyseal dysplasia in children treated with Deferoxamine before the age of 2 years, prompting recommendations for later therapy.

Wang et al., (1989) showed that starting chelation therapy late will cause chronic iron overload in patients with severe Thalassaemia leading to variable degrees of hypogonadotropic hypogonadism. Another study indicated that combined multiple transfusions and chelation therapy preserved the integrity of the ACTH-cortisol axis in patients with Thalassaemia (Sklar et al., 1987). It was found that growth hormone responses to glucagon stimulation were significantly impaired

in all of the patients with iron overload (Grundy et al., 1986). In parallel, a striking increase in fertility in men and women with Thalassaemia has been reported over the last decade (Jensen, 1995).

Thalassaemia patients who used more Desferrioxamine in relationship to transfusional iron load, showed a reduction in the risk of diabetes mellitus and glucose intolerance, compared to those in whom Desferrioxamine was begun at a more advanced age and had therapy administered less intensively (Brittenham et al., 1994).

Impact on quality of life

Caro et al., (2002) described the burden of Thalassaemia major and its treatment, in terms of prevalence of iron-overload-related complications, direct and indirect costs, and the patient's physical and social well-being and their families. He concluded that there remains a need to improve the management of Thalassaemia, as many patients with iron-related complications experience physical and social limitations.

Impact on Bone Marrow Transplantation patients

Successful allogenic bone marrow transplantation (BMT) in Thalassaemia liberates patients from chronic transfusions but does not eliminate the necessity for iron-chelating therapy in all patients. Short-term Desferrioxamine is safe and effective in the reduction of tissue iron in the "ex-thalassaemic" patient, and should be initiated 1 year after successful marrow transplantation if the hepatic iron concentration exceeds 7 mg iron/gram liver tissue, dry weight, at that time.(ref?)

Compliance with Desferrioxamine and alternatives to subcutaneous infusion.

For improvement of patient compliance, a regimen of ambulatory continuous IV Desferrioxamine with weekly change of infusion site , infusion site care and weekly clinic visits, will remove the need for nightly self-administration (Cohen et al., 1990) A high dose (6 to 12 g) IV Desferrioxamine infused daily for 12 hrs over 12 to 25 months resulted in decrease serum ferritin levels of56% to 99%. Liver iron concentrations, measured by magnetic susceptibility in two patients, were 1234 and 2438 micrograms/gm wet weight (22.1 and 43.6 mumol/gm wet weight) after treatment for 17 and 25 months, respectively. Patient with congestive heart failure or severe ventricular dysarrhythmias no longer required cardiac medication after 12 to 24 months of chelation therapy (ref?).

Desferrioxamine administered by the subcutaneous route or by using infusion pumps or by rapid injection showed no significant difference in urinary iron excretion and changes in serum ferritin levels. However, the efficacies were similar, there were minimal side effects, as well as being better accepted by patients, thus improving the compliance of therapy (Di Gregorio et al., 1997).

(iii) Cost effectiveness

A local study of cost requirements showed that initiation of chelation therapy in transfusion dependent patients is undoubtedly a cost effective intervention (Khuzaiah & Shekar – unpublished).

Ginsberg et al., (1998) suggested that usage of the oral chelator which is cheaper would improve the benefits ratio as Desferrioxamine is more expensive with its attendant home infusion service costs.

It can be concluded that there is sufficient evidence to support the use of Desferrioxamine and it is effective in preventing or improving serious complications.

6.3.3 Oral Deferiprone *(L1)*

(i) Safety

Deferiprone *(L1)* is a safe oral iron-chelating agent that decreases iron overload without causing considerable side-effects (Rombos et al 2000; Barman Balfour & Foster 1999), and is safe if used under strict supervision, in transfusion-dependent iron overloaded children (Lucas et al., 2000, Cohen, 2000). The overall toxicity is comparable to that of Desferrioxamine in both animals and humans (Kontoghiorghes et al., 2000)*)*. Most studies found that the toxic side effects of the use of L1 were agranulocytosis (0.6%), musculoskeletal and joint pains (15%), gastrointestinal complaints (6%) and zinc deficiency (1%). However, the incidence of these toxic side effects are currently considered reversible, controllable and manageable, by using lower doses of L1 or combination therapy with Desferrioxamine (Kontoghiorghes et al., 2000, Taher et al., 1999, Cohen et al., 1998). It was also found that the combination therapy could benefit patients experiencing toxicity with Desferrioxamine, and those not responding to either chelator alone. Studies also found that Deferiprone

However, one study found that Deferiprone may worsen hepatic fibrosis in patients with Thalassemia (Olivieri et al., 1998). However, it has been suggested that additional studies using larger numbers of Deferiprone-treated patients are essential to determine safety of this drug, particularly in relation to the development of fibrosis (Richardson, 2001).

With respect to immuno-suppression or immunodeficiency, no clinical or laboratory changes consistent with this has been observed during Deferiprone therapy (Loebstein et al., 1997).

Despite the steady progress in iron chelation therapy with Desferrioxamine and L1, further investigations are required for optimising their use in patients by selecting improved dose protocols, and by minimising their toxicity (Kontoghiorghes et al.,2000).

(ii) Dose and route of administration

It has been found that oral doses of 50-120 mg/kg/day, or dose of $\geq$ 75mg/kg/day are is more effective than lower doses (Kontoghiorghes et al., 2000, Lucas et al., 2000, Rombos et al., 2000, Barman Balfour & Foster, 1999, Addis et al., 1999).

***(*iii) Effectiveness**

L1 is a clinically available oral iron chelator which has been taken by over 6000 patients worldwide, in some cases daily for over 10 years with very promising results. L1 was able to bring patients to a negative iron balance at a dose of 50-120 mg/kg/day, by increasing urinary iron excretion, decreasing serum ferritin levels and reducing liver iron in the majority of chronically transfused iron-loaded patients (Kontoghiorghes et al., 2000, Barman Balfour & Foster, 1999, Addis et al., 1999). Another study showed that HCV-negative patients exhibited a significant decrease in serum ferritin after 6 and 12 months of Deferiprone therapy (Taher et al., 1999). It was found that in patients inadequately chelated by daily dose of Deferiprone of 75 mg/kg body weight, increasing the dose of Deferiprone, or combining subcutaneous Desferrioxamine with Deferiprone therapy improves the efficacy chelation (Wonke et al., 1998). The sequential use of Deferiprone and Desferrioxamine in children with Thalassaemia major showed no significant decline in serum

ferritin, however, there is a significant reduction in hepatic iron concentration and hepatic activity index in liver tissues of the patients at the 6th month of the sequential therapy, whereas fibrosis scores did not differ significantly (Aydinok et al., 1999). It has also been reported that Deferiprone does not adequately control body iron burden in patients with Thalassemia (Olivieri et al., 1998).

CONCLUSIONS

There is sufficient evidence to conclude that Deferiprone is a safe and effective oral iron-chelating agent that can be used, under supervision, in transfusion-dependent iron overloaded children. It decreases iron overload without causing considerable side-effects, since the evidence shows that the possible risk of toxicity are reversible, controllable and manageable. The recommended oral dose is more than 75mg/kg/day.

6.3.4 Transplantation

(i) Safety

It has been found that there is a higher incidence of fulminant sepsis and growth impairment in bone marrow transplantation (BMT) patients (Piga et al., 1998). The late effects of BMT are almost equal to the adverse effects of iron overload in patients with conventional transfusion and chelation therapy (Mentzer, 2000).

(ii) Effectiveness

Sibling donor bone marrow transplantation

Studies in Pesaro, Italy identified 3 risk classes based on the presence or absence of three parameters, namely, hepatomegaly, portal fibrosis and high ferritin level. Those with all three parameters absent were classified as class 1, those with one or two parameters were classified as class II, and those with all three parameters present as class 3. It was found that there were significant differences in survival rates among the three risk groups as shown in Table 1 below: (Lucarelli et al., 1998, 1993; Giardini et al., 1994,Glardini et al., 1995)

Table 1: Bone Marrow Transplantation inpatients with Thalassaemia :

Study	**Probability of survival (%)**			**Event-free survival (%)**			**Rejection (%)**			**Non- rejection mortality (%)**		
Class	*I*	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*
Lucarelli et al 1998	95	85	78	90	81	54	5	15	33	5	4	19
Lucarelli et al 1993	92	-	-	85	-	-	6	-	-	8	-	-
Giardini et al 1994	97	84	54	94	81	49	-	-	-	-	-	-
Giardini et al 1995	90	88	55	90	85	53	5	4	9	5	12	42

The survival rates were reported to range from 51 – 94% (Walters et al., 1994, Ghavamzadeh et al., 1998, Lucarelli et al., 1999, Menszer et al., 2000, Chan et al., 2001, Vellodi et al., 1994) while disease-free survival ranged from 57 – 79% (Walters et al., 1994, Lucarelli et al., 1999, Menszer et al., 2000, Chan et al., 2001). It was also found that the risk factors influencing the survival rate

after BMT were patients with liver toxicity, those who were poorly chelated, those in the older age group (> 9 years old), presence of portal/liver fibrosis and increasing serum ferritin, and those with hepatitis infection (Ghavamzadeh et al., 1998, Lucarelli et al., 1999, Chan et al., 2001).

The survival rates ranged from 76%- 91% while disease-free survival rates of 53%-87% have been reported by various centres (Table 2).

Table 2: Reported Transplants for Thalassaemia and Probabilities of Survival and Disease Free Survival in Various International Centres (adapted from An NY Acad Sciences)

Centre	**Patients**	**Survival (%)**	**Disease free survival (%)**
Pescara	102	91	87
USA	68	87	70
UK	50	90	76
Teheran	60	83	73
Malaysia	28	86	75
Hong Kong	25	86	83
Bangkok	21	76	53

Piga et al., (1998) found that the overall survival at the age of 25 years for conventionally treated patients with good chelation therapy was 99%, whereas for those who underwent bone marrow transplantation it was 82 % (Table 3).

Table 3: Comparison of survival rates between BMT and conventional therapy at the age of 25 years

Type of intervention	**No of patients**	**Survival Rate (%)**
Bone Marrow Transplantation	32	82
Conventional Therapy with high chelation	111	99
Conventional Therapy with low /no chelation	44	70

Another study reported a similar disease free survival in patients receiving regular blood transfusion and chelation therapy, and the Pesaro Class 1 bone marrow transplant patients of 91% and 90% respectively. However, the continuing high cost of blood transfusions and chelating therapy makes it a more expensive option compared to bone marrow transplantation (Olivieri et al., 1994).

It has been reported that class I patients will achieve relatively normal iron distribution 1 or 2 years after BMT (Lucarelli et al., 1998, 1993, Giardini et al., 1994), and that continued use of chelating agents help in the removal of deposited iron in young patients after BMT. However in the older ex Thalassaemics, phlebotomy is the treatment of choice (Lucarelli et al., 1998).

The administration of Busulphon and Cyclophosphamide, in certain cases, total body irradiation, and the use of graft versus host-disease prophylaxis with Cyclosporine, Methotrexate and Antilymphocyte globulin have shown an improvement in survival rates, but was followed by higher rejection rates (Walters et al., 1994, Giardine et al., 1995, Lucarelli et al., 1999).

Bone marrow transplantation from unrelated donors and alternative donors

Finding suitable related donors is often difficult, since only 25 % of patients with Thalassaemia have histocompatible siblings, and there is high morbidity in using unrelated donors (Kelly 1997). The limited related HLA matched donors hampers the success of BMT and this results in high graft versus host disease and mortality (Lucarelli et al., 1993, Giardini et al., 1994, 1995; Vellodi et al., 1994, Gaziev et al., 2000). However, it has been reported that 69% patients remained alive and transfusion dependent, while there was a 12 % rejection rate in those who received BMT from unrelated donors (La Nasa et al ., 2002).

Cord blood transplantation

Umbilical cord blood has been found to contain hematopoietic stem cells that are capable of reconstituting bone marrow, and can be used for transplantation in both related and unrelated donors (Woodard et al., 2002).

Kelly et al (1997) found a lower incidence of GVHD with the use of umbilical cord blood compared to bone marrow transplant, although the engraftment rates of both are similar. In Thailand, a case study reported successful use of HLA identical donor umbilical cord blood in a child with HbE-beta-Thalassaemia (Issaeagrisil et al., 1994). A similar success has also been reported in Malaysia (Chan et al., 1999).

The success of umbilical cord blood transplantation has led to the suggestion of the setting up of banks for preserving umbilical cord blood for those who do not have HLA matched siblings. However, many ethical issues need to be addressed (Kelly, 1997). In the US, there is a public funded cord blood programme assisting in the collection of cord blood to facilitate transplants among sibling donors (Reed, 2000).

Peripheral blood stem cell transplantation

For peripheral blood stem cell transplantation using phenotypically identical donors, the event free survival was 86.6% (Yesilipek et al., 2001). It has been reported that engraftment was found in all patients who received peripheral blood stem cell transplantations from HLA-identical siblings (Fang et al., 2002).

CONCLUSION

There is sufficient evidence that sibling donor bone marrow transplantation is effective, while there is also evidence of effectiveness of cord blood transplantation and peripheral blood stem cell transplantation.

6.*3.5 Other treatment modalities*

(i) Augmentation of Fetal Hemoglobin Synthesis

The drugs used to increase HbF are those that inhibit the proliferation of cells as in the treatment of cancer like Hydroxyurea, 5-Azacytidine etc.

(a) ***Hydroxyurea***

The administration of Hydroxyurea to multi transfused Indian children has shown insignificant increase of total Hb and Hb F (Choudry et al., 1997). However, Arruda et al., (1997) reported a significant increase in a case study. In the treatment of Thalassaemia intermedia, Hajjar and Pearson (1994) demonstrated an increase of total Hb in 3 adult patients. Another study by Zeng et al (1995) showed an increase in total Hb and HbF in 2 Chinese patients with a resultant better quality of life. A prospective trial involving 8 Cypriot and Greek patients showed an increase in Hb F, larger red cells, increases in MCH and a sense of " feeling better " after commencement of Hydroxyurea (Loukopoulos et al., 1998). Another study on the use of Hydroxyurea in Thailand, found an increase of 33% in Hb F, a 59% decline of Hb E and a slight increase in total Hb (Fucharoen et al., 1996).

(b) ***5 Azacytidine***

A case report of the use of IV 5 Azacytidine (5-AzaC) in 3 patients with terminal Thalassaemia showed an increase in hemoglobin levels, with 2 patients being transfusion free with a better quality of life. One patient, however, withdrew due to personal reasons and subsequently died (Lowrey et al., 1993).

(c) ***Butyrates***

Perrine et al., (1993) reported encouraging results in 6 patients with IV Arginine butyrate. , Another study on the use of oral Phenylbutyrate demonstrated limited use of it in some patients who are not transfusion dependent (Collins et al 1995)., However, a study on 10 patients with extended use of IV Arginine butyrate failed to show any increase in total hemoglobin and Hb F (Sher et al, 1995). Reich et al (2000) also failed to show any substantial evidence of its ability in raising the total Hb in patients with Thalassaemia intermedia.

(d) ***Erythropoietin***

Rachmilewitz et al (1998) found that Erythropoietin is possibly effective when used either alone, or in combination, on Thalassaemics especially in splenectomized patients. The magnitude of response corresponds to the dose used.

(e) ***Combination Agents***

Olivieri et al., (1997) demonstrated that the combination of Sodium phenylbutyrate and Hydroxyurea was able to minimize the need for blood transfusions in 2 siblings with Hb Lepore and red cell alloimmunisation. An ongoing study on the use of a combination of oral Sodium phenylbutyrate and Hydroxyurea in 14 patients with Thalassaemia intermedia, reported a response rate of 36% and a 50% increase in Hb in those who are not transfusion dependent (Dover et al., 1998). Another study found that although there was a significant increase of Hb and HbF levels, the effects lasted as long as the treatment was carried out and the Hemoglobin level fell once the treatment was stopped (Loukopoulos et al., ?year).

(f) ***Other agents***

Rund et al., (1998) reported the use of Heme arginate in Thalassaemia intermedia, where there was a 2-fold increase in total hemoglobin level and a 4.2 times increase of Hb F levels.

(ii) Gene Therapy

Beuzard (1997) and Blau (1998) reported that gene therapy remains largely experimental.

(iii) Nutrition, Vitamins Support

In a study by Fuchs et al., (1997) on 12 Thai Thalassaemic children, growth stunting was found to be due to reduced nutrient intake, and was alleviated after intensive nutritional support was given to these children.

Bartfay et al., (2001) in a study of 20 patients with beta Thalassaemia major suggested that there is deficiency of selenium in these patients and these may have contributed to poor quality erythrocytes. Kajanachumpol et al., (1997) when investigating the levels of zinc and copper levels in hair , erythrocyte and plasma levels in 11 patients with Hb H disease, 59 patients with beta-Thalalssaemia/hbE and 20 patients with homozygous Thalassaemia, found decreased levels of plasma and hair zinc levels, but higher plasma Copper and erythrocyte levels in patients compared to controls. The reason for this is not clear, probably due to an impairment of utilization of these trace elements in these patients.

Dietary Magnesium supplementation has been found to improve the cellular function of RBCs of Thalassaemia intermedia (De Francesechi et al., 1998).

Yesilipek et al., (1998) used L-carnitine on 19 homozygous beta Thlassaemia patients and reported an increase in transfusion interval from 4 weeks to 12-14 weeks in 2 patients.

Supplemental Vitamin E has been said to have a role in improving the oxidative stress of erythrocytes in beta-Thalassaemic intermedia individuals (Tesoriere et al., 2001).

A review suggested that hormonal replacement with growth hormone and insulin therapy, be given to children with growth reduction and to those with diabetes. For those with alloimmunisation to red blood cells transfusion, it is suggested that Corticosteroids be given (Kattamis et al., 1995).

(iv) Psychological therapy

A Cochrane review found no form of psychological therapy in the medical literature so far that would aid patients with chronic illnesses like Thalassaemia to cope with the disease (Anie, 2001).

CONCLUSION

It can be concluded that the role of modulators of fetal hemoglobin synthesis like hydroxyurea, butyrates, 5 azacitidine and erythropoietin still remain largely experimental and cannot replace the need for regular blood transfusions and regular chelation therapy. The institution of gene therapy to replace bone marrow transplant appears to be still unattainable in the near future. There is no reported medical literature on psychological support for these patients and their families.

7 CONCLUSION

There is sufficient evidence that a screening and prevention programme is effective for the control of β-thalassaemia trait. The options for effective screening include screening of 15-16 year old

school students, pre-marital screening, and screening of relatives of known carriers. Screening tests include MCH and osmotic fragility test.

The complications of Thalassaemia include Hepatitis B and Hepatitis C, cardiac complications like heart failure, short stature, pubertal delay, and osteoporosis. Other less common complications include diabetes mellitus. With respect to blood transfusion, there is sufficient evidence to conclude that leukocyte reduced red cells, produced either in the blood bank or using bed-side filters, are effective in reducing transfusions reactions, the better the filter, the greater the reduction in transfusion reactions. The use of neocytes for transfusion can decrease blood requirement, but is costly. The pre-transfusion Hb level should be not less than 9g/dL and more than 10 g/dL, so as to ensure adequate suppression of erythropoiesis (and its complications). This will reduce blood consumption and iron loading, thus ensuring a better quality of life. The transfusion interval ranges from 2-4 weeks. There is evidence that group and cross matching for ABO, Rh (CDE) and Kell antigen will reduce the incidence of red cell alloimmunisation to a very low level compared to only routine ABO and RH (D) screening. This is especially so with patients who start transfusion much later in life (> 3 years old).

For the treatment of Thalassaemia by chelation therapy, that there is sufficient evidence that Desferioxamine is effective in preventing or improving serious complications of the disease. Deferiprone is a safe and effective oral iron-chelating agent that can be used, under supervision, in transfusion-dependent iron overloaded children. It decreases iron overload without causing considerable side-effects, since the evidence shows that the possible risk of toxicity are reversible, controllable and manageable. The recommended oral dose is more than 75mg/kg/day.

With respect to transplantation, there is sufficient evidence that sibling donor bone marrow transplantation is safe and effective, and more cost effective compared to blood transfusion therapy. While sibling bone marrow transplantation is most effective, there is also evidence of effectiveness of bone marrow transplantation from unrelated and alternative donors, cord blood transplantation and peripheral blood stem cell transplantation.

The role of modulators of fetal hemoglobin synthesis like Hydroxyurea, Butyrates, 5 Azacitidine and Erythropoietin is still largely experimental and cannot replace the need for regular blood transfusions and regular chelation therapy. The institution of gene therapy to replace bone marrow transplant appears to be still unattainable in the near future. There is no reported medical literature on psychological support for these patients and their families.
There is insufficient evidence on the effectiveness of other treatment modalities like nutrition support and vitamins.

8. RECOMMENDATION

8.1 Prevention and screening programm

It is recommended that a screening and prevention programme for the control of β-thalassaemia trait be instituted. Screening of school students and screening of relatives of known carriers should be carried out. Pre-marital and prenatal screening services should be offered for those who request for it.

8.2 Treatment

8.2.1 Blood transfusion

Thalassaemic children should receive leukocyte-reduced red cells for transfusion . Use of neocytes is not recommended because of the high costs involved. All blood should be screened for ABO and Rh (D) compatibility, while Rh (C and E) and Kell may be undertaken in centers capable of carrying them out.

8.2.2 Chelation therapy

It is recommended that Desferrioxamine and Deferiprone be used to prevent or improve serious complications of the Thalassaemia. Combination therapy should be considered in patients with inadequate doses of DF due to its high cost or side-effects.

8. 2.3 Bone Marrow transplantation

Bone Marrow Transplantation should be offered to patients as soon as possible especially if there is a HLA compatible sibling/ family member. Bone marrow transplantation from unrelated and alternative donors, cord blood transplantation and peripheral blood stem cell transplantation services can also be offered where indicated.

8.2.4 Other treatment modalities

There is insufficient evidence to recommend other treatment modalities.

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EVIDENCE TABLE- MANAGEMENT OF THALASSAEMIA

Bone Marrow Transplantation

No	Author, title, Journal, Year, Vol, Page No.	Study design, Sample, Size, Follow-up	Outcome & Characteristics	Comment
1.	Angastinoitis MA (1981) Prevention of thalassaemia in Cyprus Lancet, Feb 14, pp 369-370	a)Public education 1971 b)Population screening 1973 c)Genetic counseling d)Antenatal diagnosis – referrals to other centers	Expected Actual 1974 64 51, 1979 77 18 1979 – yearly cost of prevention (including antenatal diagnosis) represents 5 weeks expenditure for treatment of patients. Cost effective Accepted. Population screening – 40% voluntary. 60% - referrals.(15-44 years)	Fair
2	Sirdah M, Bilto YY, el Jabour S, Najjar K (1998) Screening secondary school students in the Gaza strip for beta-thalassaemia trait. Clin Lab Haematol, 20(5), Oct, pp 279-83	Randomised controlled trial	A small scale screening study for beta-thalassaemia trait has been carried out in the Gaza Strip, involving 1650 secondary schools healthy students, 16-18 years old and from both sexes. The results showed that the overall prevalence in the Gaza Strip of beta-thalassaemia was 4.3%. The frequency of beta-thalassaemia trait in the microcytic (defined as MCV < or = 80fl and/or MCH < or = 26 pg) subjects was 27.1%. The efficacies of some of the proposed discrimination functions in the differentiation between beta-thalassaemia trait and non-thalassemic microcytosis were evaluated. The Mentzer index, MCV of < or = 72fl, England & Fraser DF and the Shine & Lal formula were found to correctly identify 91.6%, 82.4%, 81.3% and 62.6% of the studied cases of microcytosis as having or not having the beta-thalassaemia trait. It was concluded that both beta-thalassaemia and microcytic anaemias are major health problems in the Gaza Strip. The various forms of consanguineous marriages, in addition to poor economic conditions in the Gaza Strip may have contributed to the concentration of beta-thalassaemia and the prevalence of microcytic anaemias in this population	Good
3.	Lau YL et al (1997)	High school children	8.3% - microcytosis	

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	Prevalence and genotypes of alpha and beta thalassaemia carriers in Hong Kong – Implications for population screening NEJM, 336 (18), pp 1298-1301	2420 – 75% agreed for testing	5% - alpha thal carriers 3.4%-beta thao or E carriers Risk estimation for alpha thal dis 145 and beta thal 80 per year in pregnant women but about half are refereed for PND Many at risk are not referred for genetic counseling. Need for community based program for education, screening and counseling	
4.	Ostrowsky J (1985) Cost benefit analysis of a thalassaemia disease prevention program AJPH, 75(7), pp 732-736	a)Screens-80% of at risk persons in high risk communities b)Provides diagnosis to 75% of at risk couples c)Prevented two-third of new cases	Cost of medical and public health resources both incurred and avoided resulting from use of these prevention services -- total direct cost per case prevented in the program is less than cost for a single year of treatment for an individual with disease.	Confirmed cost effectiveness of the program
5	Younis K. (2002) Situation of Beta Thalassaemia major in West bank/ Palestine Sept 2002: TIF-1st International Association Workshop. Nicosia	Country report of 420 thalasseamics of which 50% are iron overloaded due to poor compliance to chelation. 77% due to consnagunity. 20 –25 new cases per year. 69 families with more than 1 child affected.	Premarital testing for thalasseamia has become mandatory by law since May 2000. Ministry of Education has also started screening for 7th Grade students since 2001.	1st Arab world country to introduce mandatory premarital testing.
6	Dhamcharee V, Romyanan O, Ninlagarn T. (2001) Genetic counseling for thalassemia in Thailand: problems and solutions. Southeast Asian J Trop Med Public Health, 32(2), Jun, pp 413-8	Survey	Thalassemia, a hereditary anemia, has been a major public health problem in Thailand and Southeast Asia for decades, yet the prevalence of thalassemia in Thailand is not decreasing due to lack of awareness of this disease in Thai population, which implied that genetic counseling was a failure. We determined the problems and obstacles in thalassemia counseling in Thailand and proposed the possible solutions in order to deliver genetic counseling and services to the communities more efficiently. A survey in thalassemia services was	Poor

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			carried out in 12 hospitals; 9 in Bangkok, 3 in the North, Northeast, and South of Thailand respectively, by using questionnaire designed to assess the healthcare system, characteristics of target population, methods of genetic counseling, knowledge and attitudes of counselors, thalassemia support group, and researches in thalassemia, in a cross-sectional descriptive research design. The main problems in genetic counseling for thalassemia in Thailand are the followings; thalassemia problems not visible to the administrators, unorganized teamwork and services, lack of knowledge and inadequate numbers of counselors, lack of thalassemia support group, and inadequate researches in thalassemia prevention and control. The possible solutions are proposed. This study has pointed out the unseen problems and obstacles, along with the solutions in genetic counseling, given correctly, will help create awareness of thalassemia impact on health and socioeconomics in the Thai population. Thus, genetic counseling, with well-established guidelines, is a critical component for the success of prevention and control of thalassemia in Thailand.	
6	Cao A, Rosatelli MC, Galanello R. Population based genetic screening Current Opinion in Genetics and Development 1991, 1: 48-53	One person in 8 in Sardinia is a carrier for β-thalassemia. One in 60 couples have both parents as carriers.	One newborn in 250 life-births has homozygous β-thalassaemia major. Single α-thal gene deletion is present in 35.9% which may confuse carrier identification. In order not to miss these double heterozygotes in all cases (MCV/MCH and Hb A2 levels are done). A problem in this population were double heterozygous state for both δ and β-thal gene, δβ-, and γδβ-thalassemia where the Hb A2 levels are normal	
7	Mitchell JJ, Capua A, Clow C, Scriver CR (1996)	N= 14,844	we screened 14,844 Ashkenazi-Jewish students, identified 521 HexA-deficient carriers (frequency	Poor

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	Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassemia disease carriers in high schools. Am J Hum Genet,59(4), Oct, pp793-8	F/up: 1972-1992	1:28), reached 89% of the demographic cohort in the educational component of the program, and achieved 67% voluntary participation in the subsequent screening phase. The corresponding data for the beta-thalassemia program are 25,274 students (mainly of Mediterranean origin) representing 67% of the cohort with 61% voluntary participation in the screening phase (693 carriers; frequency 1:36). From demographic data, we deduce that virtually all the carriers identified in the high-school screening program remembered their status, had their partner tested if they did not already know they were a carrier couple, and took up the options for reproductive counseling/prenatal diagnosis. In Montreal, the current origin of all couples using prenatal diagnosis for Tay-Sachs and beta-thalassemia diseases is the corresponding genetic screening/testing program, whereas, at the beginning of the programs, it was always because there was a history of an affected person in the family. Incidence of the two diseases has fallen by 90%-95% over 20 years; the rare new cases are born (with two exceptions) outside the target communities or to nonscreened couples.	
8	Lena-Russo D, Badens C, Aubinaud M, Merono F, Paolasso C, Martini N, Mattei JF (2002) Outcome of a school screening programme for carriers of haemoglobin disease. J Med Screen, 9(2), pp 67-9	Evaluation study	RESULTS: Half of the carriers replied to the questionnaire: 86% knew that they have to test their partner. Six carrier couples were identified, four asked for genetic counselling and requested eight prenatal diagnoses, two couples did not request genetic counselling and have had two affected children. CONCLUSIONS: Despite the time lapse between screening, informing, and pregnancy (mean 15 years), the information was well conserved and resulted in testing of the partner. The	Poor

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			screening programme was effective in motivating requests for prenatal diagnosis.	
9	Ghanei M, Adibi P, Movahedi M, Khami MA, Ghasemi RL, Azarm T, Zolfaghari B, Jamshidi HR, Sadri R. (1997) Pre-marriage prevention of thalassaemia: report of a 100,000 case experience in Isfahan. Public Health,;111(3), May, pp153-6	N= 10,000 F/up: Jan 1993 – Jan 1996	After the project had been running for three years the average of high risk couple initially deciding not to marry was 90% and no new cases of thalassemia were detected in the children of the screened population. Where both members of the couple were trait-positive their preferred choice was not to marry, rather than to marry and use other or no methods of preventing a thalassemia affected child being born to them. Cultural and religious ideas can affect such decisions and in some Islamic countries the establishment and use of a genetic counselling centre can help prevent most of new thalassaemia cases.	Poor
10	Ahmed S, Saleem M, Sultana N, Raashid Y, Waqar A, Anwar M, Modell B, Karamat KA, Petrou M. (2000) Prenatal diagnosis of beta-thalassaemia in Pakistan: experience in a Muslim country. Prenat Diagn, 20(5), May, pp 378-83	Not stated	A service for prenatal diagnosis of beta-thalassaemia was introduced in Pakistan in May 1994. Two renowned Islamic scholars, consulted before the service was introduced, ruled that a pregnancy can be terminated if the fetus is affected by a serious genetic disorder, and if termination is before 120 days (17 weeks) of gestation. During the first 3(1/2) years of the service 300 couples requested the test. Almost all the couples had been informed by their treating doctors. Most diagnoses were made between 10 and 16 weeks of gestation, and only 15 (5%) were reached after the 16th week. DNA analysis was by the amplification refractory mutation system (ARMS). A multiplex ARMS was developed in which three primer combinations identified the mutations in 91.5% of the couples. In 13 couples (4.	Poor

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			3%) linkage analysis was required for the fetal diagnosis. In 47/53 (88.7%) women carrying an affected fetus the pregnancy was terminated. In six cases it was declined principally on religious grounds. Postnatal confirmation of the prenatal diagnosis was possible in 117 unaffected children. One year after the start of the service, interviews with 141 couples with an affected child showed that 72% knew of the availability of prenatal diagnosis. Thirty-two of the informed couples had had a pregnancy, but only 18 (56%) used prenatal diagnosis. The main reasons for non-utilization of prenatal diagnosis were the cost of the test and fear of undergoing the test, though some gave no clear explanation. This study demonstrates that prenatal diagnosis is feasible and acceptable in a Muslim country such as Pakistan	
11	Zahed L, Bou-Dames J. (1997) Acceptance of first-trimester prenatal diagnosis for the haemoglobinopathies in Lebanon. Prenat Diagn, 17(5), may, pp423-8	Interview N= 83 couples at risk for a haemoglobin disorder	mostly beta-thalassaemia, in an effort to evaluate their attitude towards first-trimester prenatal diagnosis. Most of the families had received poor education and were of low socio-economic status and more than half of the couples were not properly aware of their genetic risk. Fifty-nine per cent of the couples were definitely in favour of prenatal diagnosis, 23 per cent were uncertain at the time of the interview, and 18 per cent were opposed to such testing, because of their religious conviction against termination of a pregnancy. Another important factor which seems to influence choice was the cost of the test. Essential issues that arise from this study include the importance of a control programme adapted to particular populations, proper information and counselling, and the need for financial support in countries such as Lebanon.	Poor

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12	Sangani B, Sukumaran PK, Mahadik C, Yagnik H, Telang S, Vas F, Oberroi RA, Modell B, Merchant SM. (1990) Thalassemia in Bombay: the role of medical genetics in developing countries. Bull World Health Organ, 68(1), pp 75-81	Not stated	This study of 200 families with thalassaemic children in Bombay showed that these children's treatment and needs place a significant, unavoidable and increasing demand on the public health services. At the same time, owing to the potentially large number of patients and the difficulties of long-term management, the situation is characterized by evasion of the problem, failure of planning, no provisions for prevention, and inadequate treatment leading to premature death among the affected children. The burden on such families is greater in developing than in developed countries because, besides caring for the chronically sick child, their lives are dominated by the high costs of treatment, often amounting to 20-30% of the income for many families. Seven mothers with no healthy children and 27 with only one healthy child had been sterilized; 90% of reproductive-age couples felt that prenatal diagnosis was a necessity. Also, ignorance and prejudice in the community led to social isolation for forty families. The experience in Europe shows that improved treatment is the key step in controlling thalassaemia. A well-organized day-transfusion service is cost-effective, soon restoring the children to health and leading to increased optimism. The formation of associations by parents could mobilize community support for improved treatment and prevention, and increase public awareness of the problem. Thus cost-effective management and prevention through screening, genetic counselling, and prenatal diagnosis are at least as important in the developing as in developed countries.	

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13	Chadwick R, ten Have H, Husted J, Levitt M, McGleenan T, Shickle D, Wiesing U (1998) Genetic screening and ethics: European perspectives. J Med Philos,23(3), Jun, 255-73		Analysis and comparison of genetic screening programs shows that the extent of development of programs varies widely across Europe. Regional variations are due not only to genetic disease patterns but also reflect the novelty of genetic services. In most countries, the focus for genetic screening programs has been pregnant women and newborn children. Newborn children are screened only for disorders which are treatable. Prenatal screening when provided is for conditions for which termination may be offered. The only population screening programs for adults are those for thalassaemia carrier status in Cyprus, Greece and Italy. Social responses to genetic screening range from acceptance to hostility. There is a fundamental tension between individual and community in the debates in various European countries about implementation of screening programs. Opposition to genetic screening is frequently expressed in terms of arguments about "eugenics" with insufficient regard to the meaning of the term and its implications. Only a few countries have introduced explicit legislation on genetic screening. Legislation to address discrimination may provide more safeguards than legislation protecting genetic information itself.	Poor
14	Petrou M, Modell B, Shetty S, Khan M, Ward RH. (2000) Long-term effect of prospective detection of high genetic risk on couples' reproductive life: data for thalassaemia.	N=102	Prospective risk detection with availability of prenatal diagnosis is the best service currently available for couples at high genetic risk Here we describe the long term effect of this service on the reproductive life of 102 couples at risk of thalassaemia, whose risk was detected prospectively by carrier screening, who made use	Poor

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	Prenat Diagn, 20(6), Jun, pp 469-74		of prenatal diagnosis, and where the woman is now over 40. Overall outcome for couples is described in terms of number of favourable versus unfavourable pregnancy outcomes. (A favourable pregnancy outcome = unaffected livebirth, or affected livebirth resulting from informed parental choice.) The 102 couples had a total of 356 pregnancies, including 302 viable pregnancies, and 88% achieved a family unburdened by thalassaemia. 68% of viable pregnancies had a favourable outcome, but only 43% of couples had only favourable outcomes, and 26% lost two or more viable wanted pregnancies. When early losses are included 58% of pregnancies had a favourable outcome, but only 30% of couples had only favourable outcomes, and 41% lost two or more pregnancies. Even with the best available service, at risk couples remain victims of chance, and a significant minority experience great difficulty in obtaining even one healthy child. Research is needed on approaches that may allow couples better control of reproductive outcomes.	
15	Ginsberg G, Tulchinsky T, Filon D, Goldfarb A, Abramov L, Rachmilevitz EA. (1998) Cost-benefit analysis of a national thalassaemia prevention programme in Israel. J Med Screen,5(3), pp120-6	Not stated	OBJECTIVE: In Israel (population 5.7 million) there are around 200 known living subjects with thalassaemia major, of whom around 80% are from the northern district. This study aims at examining the costs and benefits of a national screening programme to prevent thalassaemia in Israel. MEASUREMENTS AND MAIN RESULTS: The lifetime healthcare costs of caring for a person born with thalassaemia major are $284,154. The costs of the home infusion service (33.1%) actually exceed the costs of the chelating agent itself (22.1%). The remaining 44.8% of costs are due to stay in	Poor

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			hospital, operations, outpatient visits, laboratory tests, therapists, etc. Lost earnings and premature mortality costs account for a further $51,843 and $141,944 respectively for each case. A national screening programme would cost $900,197 and prevent around 13.4 homozygotes being born, at a cost of $67,369 for each birth prevented. The benefit-cost ratio of the programme to the health services is 4.22:1, which increases to 6.01:1 when a societal perspective is taken. However, around 13.0 homozygote births are still expected to occur, the majority owing to lack of compliance of patients at various stages in the screening process. The addition of a national health education programme for the higher risk non-Jewish population either nationally or in selected regions will incur extra costs, which may be covered by increased benefits as a result of better compliance with the screening programme. CONCLUSION: Israel should start to provide a nationwide thalassaemia screening programme as the monetary benefits to society (and even to the health services alone) will exceed the screening programmes costs.	
16	Karnon J, Zeuner D, Brown J, Ades AE, Wonke B, Modell B. (1999) Lifetime treatment costs of beta-thalassaemia major. Clin Lab Haematol, 21(6), Dec, :377-85		Beta-thalassaemia major is a serious genetic disorder, which results in a considerable increase in both acute and chronic morbidity, and mortality. Although beta-thalassaemia major is a rare disease affecting approximately 600 people in the UK, treatment is intensive and predictions of the costs incurred may aid health care planning. In this report, the cost to the health service of providing treatment services for beta-thalassaemia major patients, over the course of a lifetime, is calculated	

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			in order to assist resource allocation decisions. A cost model was developed, incorporating data from disparate sources. The undiscounted lifetime cost of treating a beta-thalassaemia major patient was estimated to be pound 803,002, although when the costs were discounted at a rate of 6%, the lifetime cost was reduced to pound 219,068. Within sensitivity analyses, the discounted cost ranged from approximately pound 188,000 to pound 226,000. This report may act as a guide to those involved in the planning of health care provision with regard to the resources required to treat beta-thalassaemia major patients. Such information may also be incorporated into the decision-making process for the provision of antenatal screening programmes for beta-thalassaemia major.	
17	Saxena A, Phadke SR. (2002) Feasibility of thalassaemia control by extended family screening in Indian context. J Health Popul Nutr, 20(1), Mar, pp 31-5	N= 100	Thalassaemia is one of the most common genetic disorders in India. Its control is possible by screening of general population for carrier status and by antenatal diagnosis in couples at risk of having a child with thalassaemia. This study explored the feasibility of screening the extended family to detect carriers to prevent birth of thalassaemic children and identified the barriers to its acceptance. One hundred parents with thalassaemic child on a regular hypertransfusion programme were interviewed using a pre-designed questionnaire. The results showed that 96% of them were more willing to share information on their thalassaemic children with relatives and friends. Relatives of 62 parents accepted the risk of being a carrier, and 14 families got themselves tested for it so far. Another 34 families could not get themselves tested due to non-availability of screening facilities	Poor

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			in the nearby town, high cost of the test, and lack of sufficient motivation. It is concluded that, by and large, parents have no reservations in sharing information on their affected children with their relatives, but the communication needs to be improved for all families to accept the risk of having a thalassaemic child. There is also a need to make the screening more readily available and to motivate high-risk groups through awareness-raising programmes.	
18	Shaike S, Hafadh N, Serafi S (2001) Premarital counseling: an experience from Bahrain EMHJ, 3(3), pp 415-419	N= 500 F/Up; 1993-1994	SCD 1.6% SCT 13% Beta Thal trait 2% G6PD 26% 8.1% of couples at risk for diseased infant Consangunity 15% Premarital counseling should be compulsory by law but freedom to act upon advice should be ensured	Poor
19	British Society for haematology (1998) Guidelines for haemoglobinopathy screening Clin Lab Haematol 10, pp 87-94	Guidelines	British committee for standardsin haematology guidelines recommends MCH as the parameter for screenin, as the first step where a value <27 pg indicates the need to quantify Hb subtypes (HPLC, value >4% as alph thal trait	Good

HIV, HCV and HBV INFECTION IN THALASSAEMICS

No.	Author, Title, Journal, Year, Volume	Study design, Sample size, Follow-up	Outcomes and characteristics	Comments
1	Al-Sheyyab M. Batieha A. El-Khateeb M. (2001) The prevalence of hepatitis B, hepatitis C and human immune deficiency virus markers in multi-transfused patients. Journal of Tropical Pediatrics, 47(4), Aug, pp 239-42	Cross-sectional N=143	0% HIV +ve 40.5% HCV +ve 3.5% HBV +ve	Poor
2	Jamal R. Fadzillah G. Zulkifli SZ. Yasmin M. (1998) Seroprevalence of hepatitis B, hepatitis C, CMV and HIV in multiply transfused thalassemia patients: results from a thalassemia day care center in Malaysia. Southeast Asian Journal of Tropical Medicine & Public Health, 29(4),Dec, pp 792-4,	Cross-sectional N=85	0% HIV +ve 22.4% HCV +ve 1.2% HBV +ve	Poor
3	Sur D. Chakraborty AK. Mukhopadhyay SP. (1998) Dr. P. C. Sen Memorial Award Paper. A study of HIV infection in thalassaemia patients of rural Bengal. Indian Journal of Public Health.; 42(3), Jul-Sep,pp 81-7	Cross sectional N=330	0.9% HIV +ve	Poor

No.	Author, Title, Journal, Year, Volume	Study design, Sample size, Follow-up	Outcomes and characteristics	Comments
4	Kumar RM. Uduman S. Hamo IM. Morrison J. Khaurana AK. (1994) Incidence and clinical manifestations of HIV-1 infection in multitransfused thalassaemic Indian children. Tropical & Geographical Medicine, 46(3), pp163-6	Cross Sectional N=406	8.9% HIV +ve	Poor
5	Sen S. Mishra NM. Giri T. Pande I. Khare SD. Kumar A. Choudhry VP. Chattopadhya D. Kumari S. Malaviya AN. (1993) Acquired immunodeficiency syndrome (AIDS) in multitransfused children with thalassemia. Indian Pediatrics, 30(4), Apr, pp 455-60	Cross Sectional N=203	8.9% HIV +ve	Poor
6	Costagliola DG. Girot R. Rebulla P. Lefrere JJ. (1992) Incidence of AIDS in HIV-1 infected thalassaemia patients. European and Mediterranean W.H.O. Working Group on Haemoglobinopathies and Cooleycare. British Journal of Haematology, 81(1), May, pp 109-12	Prospective N= 79	1.4% HIV+ve (1yr) 9.0% HIV+ve(5yr)	Fair

No.	Author, Title, Journal, Year, Volume	Study design, Sample size, Follow-up	Outcomes and characteristics	Comments
7	de Montalembert M. Costagliola DG. Lefrere JJ. Cornu G. Lombardo T. Cosentino S. Perrimond H. Girot R. (1992) Prevalence of markers for human immunodeficiency virus types 1 and 2, human T-lymphotropic virus type I, cytomegalovirus, and hepatitis B and C virus in multiply transfused thalassemia patients. The French Study Group On Thalassaemia. Transfusion,; 32(6), Jul-Aug, pp 509-12	Cross sectional N=305	0.03% HIV +ve 30% HCV +ve	Poor
8	Mozzi F. Rebulla P. Lillo F. Varnier OE. Biadati C. Calcagno L. Melotti S. Sirchia G. (1992) HIV and HTLV infections in 1305 transfusion-dependent thalassemics in Italy. The COOLEYCARE Cooperative Group. AIDS , 6(5),May, pp 505-8,	Cross Sectional N=1305	2.76% HIV+ve	Poor
9	Moatter T. Adil S. Haroon S. Azeemuddin S. Hassan F. Khurshid M. (1999) Prevalence of hepatitis G virus in Pakistani children with transfusion dependent beta-thalassemia major. Indian Journal of Pathology & Microbiology, 42(4), Oct, pp 475-82	Cross Sectional N=100	35% HCV +ve	Poor

No.	Author, Title, Journal, Year, Volume	Study design, Sample size, Follow-up	Outcomes and characteristics	Comments
10	Laosombat V. Pornpatkul M. Wongchanchailert M. Worachat K. Wiriyasatienku A. (1997) The prevalence of hepatitis C virus antibodies in thalassemic patients in the south of Thailand. Southeast Asian Journal of Tropical Medicine & Public Health, (1), Mar, pp 149-53	Cross sectional N=101	23.8% HCV +ve	Poor
11	el-Nanawy AA. el Azzouni OF. Soliman AT. Amer AE. Demian RS. el-Sayed HM. (1995) Prevalence of hepatitis-C antibody seropositivity in healthy Egyptian children and four high risk groups. Journal of Tropical Pediatrics, 6, Dec,pp 341-3,.	Cross Sectional N=18	44% HCV+ve	Poor
12	Isahak I. Baharin R. Hakim AS. Abu Bakar M. George E. (1993) Antibody to hepatitis C virus in thalassemia patients. Malaysian Journal of Pathology, 5(1), Jun, pp 85-7	Cross Sectional N=52	5.8% HCV +ve	Poor
13	Williams TN. Wonke B. Donohue SM. (1992) A study of hepatitis B and C prevalence and liver function in multiply transfused thalassemic and their parents. Indian Pediatrics,9(9), Sep, pp, 1119-24,	Case Control N=54	11.1% HCV +ve 7.4% HBV +ve Controls: 2.2% HCV+ve 11.1% HbsAg +ve	Poor

SHORT STATURE IN THALASSEMIA PATIENTS

No.	Author, Title, Journal, Year, Volume, Page No.	Study design, Sample size and follow-up	Outcomes and characteristics	Grade
1	Hamidah A, Rahmah R, Azmi T, Aziz J, Jamal R. (2001) Short stature and truncal shortening in transfusion dependent thalassaemia center in Malaysia. Southeast Asian J Trop Med Public Health, 32(3),Sept, pp 625-30	Cross-sectional study N= 66 patients	Prevalence of short stature in transfusion-dependent thalassaemic was 54.5% compared to 4.5% in control group ($p<0.001$)	Poor
2	Cavallo L, Acquafredda A, Zecchino C, De Sanctis V, Cisternino M, Caruso Nicoletti M, Galati M, Massolo F. (2001) Recombinant growth hormone treatment in short patients with thalassaemia major : result after 24 and 36 month. J. Pediatr Endocrinol Metab, 14(8), Sep-Oct, pp 1133-7	Non-randomised clinical trial N= 23 patients Follow-up : 3 years	Thalassaemia major patients with short stature should receive rhGH treatment for only one year, and that more prolonged treatment should be reserved for selected adolescents who have psychological problems due to shortness.	Good to Fair
3	Low CK, Kwan YW, Cheung PT , Li MC, Ha SY, Lau YL, Karlberg J. (1998) The effect platyspondyly and pubertal growth spurt on the stature of patients with beta-thalassaemia major. Chin Med J , 111(8), Aug, pp 731-5	Prospective with historical control N= 71 patients	27% of the boys and 32% of the girl had a height below the 3rd percentile. About 60% of all the children had a U:L ratio below the 10th percentile for age.	Good to Fair

No.	Author, Title, Journal, Year, Volume, Page No.	Study design, Sample size and follow-up	Outcomes and characteristics	Grade
4	Chrysis DC, Alexandrides TK, Koromantzou E, Georgepoulos N, Vassilakos P, Kiess W, Kratsch J, Beratis NG, Spiliotis BE. (2001) Novel application of growth hormone axis disturbances in children with beta-thalassaemia . Clin Endocrinol; 54(2), Feb, pp253-9	Cross-sectional study N= : 41 patients	IGF-I and IGFBP-3 generation tests are useful tools for the studynot only of Growth hormone insensitivity but also of GH secretory disorders.	Poor
6	Soliman AT, elZalabany M. Amer Ansari BM. (1999) Growth and pubertal development in transfution-dependent children and adolescents with thalassaemia major and sickle cell diseases: a comparative study. Journal of Tropical Pediatric, 45(1), Feb, pp 23-30	Cross-sectional study N=72 thalassaemia major patients	49% had short stature	Poor
7	Soliman AT , elZalabany MM, Mazloum Y, Bedair SM, Ragab MS, Rogol AD, Ansari BM. (1999) Spontaneous and proveked growth hormone (GH) secrection and insulin-like growth factor I (IGF-I) concentration in patients with beta thalassaemia and delayed growth. J. Trop Pediatr, 45(6),Dec, pp 327-37	Cross-sectional study	These data prove a high prevalence of defective GH secrection in thalassaemic children associated with structural abnormality of their pituitary gland.	Poor

No.	Author, Title, Journal, Year, Volume, Page No.	Study design, Sample size and follow-up	Outcomes and characteristics	Grade
8	Arcasoy A, Ocal G, Kemahli S, Berberoglu M, Yildirmak Y, Canatan D, Akcurin S, Akar N, Uysal Z, Adiyaman P, Cetinkaya E. (1999) Recombinant human growth hormone treatment in children with thalassaemia major. Pediatr Int, 41(6),Dec, pp 655-61.	Non-randomised clinical trial N= 20 patients (10 treated with growth hormone and 10 not treated)	There were significant differences between the height velocity improvements and height velocity standard deviation in the treatment group compared to the non-treatment group.	Good to fair
9	Theodorisis C, Ladis V, Papatheodorou A, Berdousi H, Palamidou F, Evagelopoulou C, Athanassaki K, Konstantoura O, Kattamis C. (1998) Growth and management of short stature in thalassaemia major. J Pediatr Endocrinol Metab; 11 (Suppl 3), pp835-44	Non-randomised clinical trial N= 143 patients 13 patients received GH therapy	8% of young boys with thal. Major aged 7-8 years have short stature. 12% of the older boys and 15% of the older girls without endocrinopathies had height <3rd percentile. This incidence was 29% when endocrinopathies were present. Role of GH in improving growth.	Good to fair
10	Caruso-Nicoletti M, De Sanctis V, Capra M, Cardinale G. (1998) Short stature and body proportion in thalassaemia. J Pediatr Endocrinol Metab.; 11 (Suppl 3), pp811-6.	Cross-sectional study N= 476	The data indicate that about 18% of thal. patients exhibit short stature; disproportion between the upper and lower body segments is present in 14% however, a short trunk despite normal stature is present in another 40% of patients. This is due to a spinal growth impairment which start in infancy and progressively aggravates.	Poor
11	Roth C, Pekrun A, Bartz M, Jarry H, Eber S, Lakomek M, Schroter W. (1997) Short stature and failure of pubertal development in thalassemia major: evidence for hypothalamic neurosecretory dysfunction of growth hormone secretion and defective pituitary ganadotropin	Cross-sectional study N=30	43.75% had short stature. Reduced GH secretion and low IGF-I in thalassaemic patients are related to a neurosecrectory dysfunction due to iron overload rather than to liver damage.	Poor

No.	Author, Title, Journal, Year, Volume, Page No.	Study design, Sample size and follow-up	Outcomes and characteristics	Grade
	secrection. Eur J Pediatr, 156(10), Oct, pp 777-83.			
12	Grundy RG, Woods KA, Savage MO, Evan JP. (1994) Relationship of endocrinopathy to iron chelation status in young patients with thalassaemia major. Arch Dis Child, 71(2),Aug , pp 128-32.	Cross-sectional study N= 18	27.8% had short stature Growth hormone responses to glucagons stimulation were significantly impaired in all of the patients with iron overload.	Poor
13	Garcia-Mayor RV, Andrade Olive A, Fernandez Catalina P et al. (1993) Linear growth in thalassaemic children treated with intensive chelation therapy. A longitudinal study. Horm Res, 40(5-6), pp 189-93	Prospective study N= 10 Follow-up : 20 years	This study reveals a positive effect of intensive chelation therapy on the linear growth in these patients.	Fair
14	Rodda CP. Reid ED. Johnson S. Doery J. Mathews R. Bowden DK. (1995) . Short stature in homozygous beta-thalassaemia major is due to disproportionate truncal shortening. Clinical Endocrinology. 42(6), Jun,587-92	Cross-sectional study N=108 patients	Short stature is due to truncal shortening	Poor
15	Kwan EY. Lee AC. Li AM. Tam SC. Chan CF. Lau YL. Low LC. (1995) A cross-sectional study of growth, puberty and endocrine function in patients with thalassaemia	Cross-sectional study N=68 patients	A cross-sectional study of growth, puberty and endocrine function was performed on 35 girls and 33 boys with thalassaemia major. **RESULT** : Despite regular transfusion and chelation therapy, 75% of the girls and 62% of the boys over the age of	Poor

No.	Author, Title, Journal, Year, Volume, Page No.	Study design, Sample size and follow-up	Outcomes and characteristics	Grade
	major in Hong Kong. Journal of Paediatrics & Child Health. 31(2), Apr, pp 83-7.		12 years were below the third percentile for height.	
16	Viprakasit V. Tanphaichitr VS. Mahasandana C. Assteerawat A. Suwantol L. Veerakul G. Kankirawatana S. Pung-Amritt P. Suvatte V. (2001) Linear growth in homozygous beta-thalassaemia and beta-thalassaemia/hemoglobin E patients under different treatment regimens. Journal of Medical Asscociation of Thailand. 84(7),July, 929-41.	Case control study 12 homozygous beta thal major and 36 cases of Hb E-beta thal. 18 of them received hypertransfusion whilst the low transfusion regimen.	The average height SDS of the hypertransfused patients was within the 50th percentile +/- 1 SD during the first decade of life in both sexes and both genotypes. Whereas, in patients who where transfused infrequently, the SDS was always below the –1 SD and decreased gradually. In severe beta-thal/Hb E cases, their growth SDS showed no difference from those with homozygous beta-thal. Normal linear growth in those with homozygous beta thal and severe beta-thal/Hb E was only seen in the group that underwent hypertransfusion and this regimen contributed to normal growth during the first ten years of life. However, adequate iron chelation and hormonal treatment in this patients were also required in order to achieve normal adult height.	Poor

CARDIAC COMPLICATIONS IN THALASSAEMIA

No.	**Author, Title, Journal, Year, Volume, Page No.**	**Study design, Sample size and follow-up**	**Outcomes and characteristics**	**Grade & Comment**
1	Sau F. Lai ME. Pargentino E. Seguro C. Pilloni MI. Kisci V. Guaita B. Naccarato S. Pisanu S. Figus R. (1995) Clinical and echocardiographic evaluation of thalassaemic cardiomyopathy Cardiologia. 40(5), May, pp 307-14,.	Cross-sectional N=103	37% cardiac impairment from CXR and ECG 28% with signs and symptoms of cardiac failure	Poor

2	Favilli S. De Simone L. Mori F. Pollini I. Cecchi F. Zuppiroli A. Manetti A. (1993) The cardiac change in thalassaemia major: their assessment by Doppler echocardiography. Giornale Italiano di Cardiologia, 23(12), Dec, pp1195-200	Case control N=25 Controls=25	12% had heart failure with cardiomyopathy	Poor
4	Richardson ME. Mathews RN. Alison JF. Menahem S. Mitvalsky J. Byrt E. Harper RW. (1993) Prevention of heart diseases by subcutaneous desferrioxamine in patients with thalassaemia major. Australian and New Zealand Journal of Medicine. 23(6), Dec, pp 656-61,.	Cross-sectional N=76 pts	51% had heart disease Risk factors: Older age, late age of using desferrioxamine, higher liver iron and serum ferritin level.	Poor
5	Anderson LJ. Holden S. Davis B. Prescott E. Charrier CC. Bunce NH. Firmin DN. Wonke B. Porter J. Walker JM. Pennell DJ. **(**2001) Cardiovascular T2-star (T2*) Magnetic resonance for the early diagnosis of myocardial iron overload. [see comments]. European Heart Journal. 22(23), Dec, pp 2171-9 .	Cross-sectional N=106 patients	All patients with ventricular dysfunction had T2* of<20ms	Poor
6	Hahalis G. Manolis AS. Apostolopoulos D. Alexopoulos D. Vagenakis AG. Zoumbus NC. (2002) Right ventricular cardiomyopathy in beta-thalassaemia major.	Cases control N= 29 patients with CHF C= 39 pts with thal major but without CHF *CHF= congestive heart failure	Majority of those with CHF demonstrated a pattern similar to that described in predominant right ventricular infarction, indicating severe right ventricular cardiomyopathy in addition to left ventricular dysfunction.	Poor

	European Heart Journal,.23(2),pp 147-56			
7	Hahalis G. Manolis AS. Gerasimidou I. Alexopoulos D. Sitafidis G. Kourakli A. Korfer R. Koerner MM. Vegenakis AG. Zoumbus NC. (2001) Right ventricular diastolic function in beta-thalassaemia major. American Heart Journal, 141(3), March, pp 428-34,.	Cases control study N= 79	In patients with homozygous beta-thalassaemia major without cardiac disease, the pattern of RV filling is abnormally altered, indicating impaired relaxation and diastolic dysfunction. In contrast, the LV filling is compatible with increased preload, as in chronic anemia. LV remodeling occurs overtime along with transition toward a restrictive ventricular filling pattern.	Poor
9	Ehlers KH. Giardana PJ. Lesser ML. Engle MA. Hilgartner MW.(1991) Prolonged survival in patients with beta-thalassaemia major treated with desferrioxamine. Journal of Pediatric,118 (4(Pt 1), Apr,pp 540-5,.	Cases control study N=71 pts with no chelation and low transfusion regime with pre-Tx Hb 7-8/dl 80 patients given hypertransfusion [pre-Tx Hb 10-11.5] and on chelation	Mean survival of those not on chelation was 17.4 years versus 31 years for those on hypertransfusion and chelation. Death was preceded by arrhythmia requiring therapy in all but one, and by cardiac failure in all.We conclude that treatment with defero xamine when used in amounts proportional to iron burden, delayed cardiac complication and improved longevity.	Poor
10	Kremastinos DT. Tsetsos GA. Tsiapras DP. Karavolias GK. Ladis VA. Kattamis CA. (2001) Heart failure in beta-thalassaemia : 5 year follow-up study. American Journal of Medicine. 111(5),Oct.1, pp349-54	Cohort N= 52 pts with heart failure.	48% survived after HF episode	Poor
11	Aessopos A. Farmakis D. Karagiorga M. Voskaridou E. Loutradi A. Hatziliami A. Joussef J. Rombos J. Loukopoulos D. (2001) Cardiac involvement in thalassaemia intermedia : a	Case control N=110 with thal intermedia and 76 controls.	Mean serum ferritin after 1657 ug/L Heart failure = 504% Pulm hypertension = 59.1%	Poor

	multicenter study. Blood. 97(11),Oct.1, pp 3411-6			
12	Borgna-Pignatti C. Rugolotto S. De Stefano P. Piga A. Di Gregorio F. Gamberini MR. Sabato V. Melevendi C. Cappellini MD. Verlato G. (1998) Survival anf disease complications in thalassaemia major. Source Annals of the New York Academy of Science. 850,Jun. 30, pp 277-31	Observational N= 1146 Those born 1960-1987	20 YSR 89% 25 YSR 82% Heart failure 6.4% Arrhythmias 5.0%	Poor
13	Borgna Pignatti C, Carnelli V, Caruso V, Dore F, De Mattia D, Di Palma A, DI Gregorio F, Romeo A, Longhi R, Mangliagli A, Melevendi C, Pizzarelli G, Musumeci S.(1998) Thromboembolic events in beta thalassaemia major: an Italian multicenter study. Acta Haematol, 99(2), pp76-9.	Multicenter prospective trial. N= 735	32 patients had thromboembolic episodes. They had a statistically significantly higher incidence of associated dysfunction including cardiomyopathy, (50 vs 13.8%).	Good to Fair
14	Kremastinos DT, Tiniakos G, Theodorakis GN, Katritsis DG, Toutouzas PK. (1995) Myocarditis in beta-thalassaemia major. A cause of heart failure. Circulation, 91(1), Jan 1, pp 66-71	Cohort study N= 1048 Follow-up : 5 years	Acute heart failure with left ventricular dysfunction (left ventricular ejection fraction, 25+/- 11%) developed in 11 patients (23.4%) with myocarditis.	Fair
15	Richardson ME, Matthews RN, Alison JF, Menahem S, Mitvalsky J, Byrt E, Harper RW. (1993) Prevention of heart diseases by subcutaneous defferioxamine in patients with thalassaemia	Cohort Study N= 74 patients	Late complication of desferrioxamine and non compliance are associated with greater iron loading and an increased risk of heart disease	Fair

	major. Aus N Z J Med, 23(6), Dec, pp 656-61.			
16	Aldouri MA, Wonke B, Hoffbrancd AV, Flunn DM, Ward SE, Agnew JE, Hilson AJ (1990) High incidence of cardiomyopathy in beta thalassaemia patients receiving regular transfusion and iron chelation: reversal by intensified chelation Acta Haemotlgica 84(3), pp 113-7	Cohort Study N= 60 patients	37% ha LVEF < 45%	Fair
17	Yaprak I, Aksit S, Ozturk C Bakiler AR, Dorak C, Turker M (1998) Left ventricular diastolic abnormalities in children with bete-thalassaemia major: aDoppler echocardiographic study Tukish Journal of Pediatrics, 40(2), pp 201-9	Case control N= 63 TM	54% LV diastolic dysfunction 13% had LV systolic dysfunction	Poor
18	Fucharoen S, Ketvichit p, Pootrakul P, Siritanaratkul N, Piankijagum A, Wasai P (2000) Clinical manifestation of beta thalassaemia/hemoglobin E disease Journal of Paediatric Hematology Oncology 22(6), Nov-Dec, pp 552-7	Case Series N= 378 HbE beta Thal	CHF = 11.9% 67% died between 20-40 yrs	Poor
19	Lombardo T, Tamburino C, Bartoloni G, Morrone ML, Frontini V, Italia F, Cordaro S, Pricitera A, Calvi V (1995) Cardiac iron overload in thalassaemic patients: an endomyocardial biopsy study	Case Series N=15TM	Significantly correlation between serum ferritin and myocardial iron grade	poor

	Annals of Hematology 71(3), Sep, pp 135-41			
20	Hou JW, Wu MH, Lin KH, Lue HC (1994) Prognostic significance of left ventricular diastolic indexes in beta thalassaemia major Archives of Paediatrics & Adolescent Medicine 148(8), Aug, pp 862-6	Cohort Study N= 45 TM pts	50% had diastolic dysfunction of these, 4 died within 2 years after onset of HF	Fair
21	Vaccari M, Crepaz R, Fortini M, Gamberini MR, Scarcia S, Pitscheider W, Bosi G (2002) Left ventricular remodeling, systolic function and diastolic function in young adults with beta-thalassemia intermedia: a Doppler echocardiograpghy study Chest 121(2), Feb, pp 506-12	Case control N=80 patients	Diastolic dysfunction seen in majority of patients compared to controls. Asymptomatic young adults with T1 show significant increases in LV volumes, LV mass, and cardiac index that are more pronounced than those in TM patients. LV systolic function is preserved in the T1 group but is slightly depressed in the TM group due to the increase of afterload and to reduced contractility	Poor
22	Wolfe L, Oliviere N, Sallan D, Colan S, rose V, Propper R, Freedman MH, Nathan DG (1985) Prevention of cardiac disease by subcutaneous desferrioxamine in patients with thalassaemia major New England Journal of Medicine 312(25; Jun20, pp 1600-3	Cohort Study N= 36 patients who started chealtion after 10 year	19 patient poor compliance of there 12 developed hear disease and 7 died mean age of HD 19 yrsa	Fair
23	Kremastinos DT, Toutouzas PK, Vyssoulis GP, Venetis CA, Avgoustakis DG (1984) Iron overload and left ventricular performance in beta thalassaemia	Cohort study N= 60 patients	14 patients were in advanced classes (III & IV) of congestive heart failure (CHF)	Poor

	Acta Cardiologica 39(1), pp 29-40			

DELAY PUBERTY IN PATIENTS WITH THALASSAEMIA

No	Author, title Journal, year, volume, page	Study design, sample size, follow up	Outcome & Characteristic	Grade & comment
1	Chatterjee R, Katz M (2001) Evaluation of gonadotrophin insufficiency in thalassaemic boys with pubertal failure: spontaneous versus provocation test J Paediatric Endocrinol Metab 14(3), Mar, pp 301-12	Cross Sectional N= 28 patients	Iron overload thalassaemia patients with failed puberty had abnormal GnRH-GTH secretory dynamics. Our data also showed that iron toxicity was the major cause of GnRH-GTH deficiency in thalassaemic patients	Poor
2	Chatterjee R, Katz M (2000) Reversible hypogonadotrophic hypogonadism in sexually infantile male thalassaemic patients with transfusional iron overload Clin Endocrinol 53(1), Jul, pp 33-42	Cross sectional N= 20 patients	Thalassamic patients with severe organ damage and iron overload are likely to be apulsatile with irreversible damage to their hypothalamo-pituitary axis, while those with less severe iron overload are likely to have potentially reversible hypogonadotrophic hypogonadism	Poor
3`	Soliman AT, El Zalabany MM, Ragab M, Abdel Fattah M, Hassab H, Rogol AD, Ansari BM (2000) Spontaneous and GnRH-provoked gonadotropin secretion and testosterone response to human chorionic gonadotropin in adolescent boys with thalassaemia major and delayed puberty J Trop Pediatric 46(2), Apr, pp 79-85	Non randomized controlled prospective trial N= 10	Hypogonadotrophic hypogonadism is themain cause of delayed/failed puberty in adolescents with thalassaemic major. Testerone replacement might be superior to HCG therapy in these patients. This therapy should be introduced at the proper time in these hypogonadal patients to induce their sexual development and to support their linear groth spurt and bone mineral accretion	Good to fair
4	George A, Bhaduri A, Choudhry VP (1997) Development of secondary sex characteristics in	Cross sectional study N= 71	The development of secondary sex characteristic in thalassaemic children is markedly delayed as compared to their non thalassaemic sibling and the	Poor

	multitransfused thalassaemic children Indian J Pediatric 64(6), Nov-Dec, pp 855-9		expected development criteria. Delay in development of secondary sex characteristics appear to be secondary to chronic hypoxia and iron overload	
5	Soliman AT el Zalabany M, Amer M, Ansari BM (1999) Growth and pubertal development in transfusion-dependent children and adolescents with thalassaemia major and sickle cell disease a comparative sudy J Trop Pediatri,c 45(1), Feb, pp 23-30	Cohort study N= 172	In thalassaemic patients between the ages of 13 and 21 years a complete lack of pubescent changes was present in 73% of boys and 42% of girls. 74% of the thalassaemic girls ad primary amenorhoea. The aetiology of impaired growth includes the contributions of lack of pubertal growth spurt due to delayed/absent puberty, decreased synthesis of IGF-1which might be secondary to a disturbed GH-IGF-1 axis and/or under nutrition	Fair
6	Filosa A, Di Maio S, Espositio G, De Marinis F, De Terlizzi F (2001) Persistance of delayed adrenarche in boys with thalassaemic J Pediatric Endocrinol Metab 14, Apr, 407-12	Cohort Study	Persistent lack of adrearche (DHEA-S 25+/- 9.5 microg/dl) in all 6 boys and the absence of pubertal sign at chronological age (CA) of 12.4 +/- yr and BA of 11.1 +/- 1.1 yr	Fair
7	Saka N, Sukur M, Bundak R, Anak S, Neyzi O Gedikoglu G (1995) Growth and puberty in thalassarmia major J Pediatric Endorinol Metab 8(3), Jul, pp 181-6	Case control study N= 54 patients	Among 11 patients over 14 years, 9 showed delay in onset or progression of puberty and 10 had growth retardation. Abnormal growth and delayed puberty are frequent in transfusion dependent thlassaemics. These can partly overcome by early of chelating therapy	Poor
8	Kwan EY, Lee AC, Li AM, Tam SC, Chan CF, Lau YL, Low LC (1995) A cross sectional study of growth, puberty and endocrine function in patients with thalassaemia major in Hong Kong	Cohort study N= 68 patients	75% of the girls and 62% of the boys over the agae of 12 years were below the third percentile for height. Hypogondotropic hypogonadism was found in a similar percentage of patients	Fair

	J Paediatric Child Health 31(2), Apr, pp 83-7			
9	Yesilipek MA, Bircan I, Oygur N, Ertug H, Yegin O, Guven AG (1993) Growth and sexual maturation in children with thalassaemi major Haematologica 78(1), Jan-Feb, pp 30-3	Cohort study	32.4% were below the third centile for height. Delay in bone age SDS was found in almost all patients, and 74.5% of the patients over 12 years of age had not yet entered puberty	Fair
10	Leheup BP, Cisternino M, Bozzola M, Dousset B, Marradi PL, Antoniozzi F, Tato L, Severi F,Sommelet D, Pierson M (1991) Growth hormone response following growth hormone releasing hormone injection in thalassaemia major: influence of pubertaldevelpment J Endocrinol Invest 14(1), Jan, pp 37-40	Cohort Study N= 35 patients	The pubertal pattern of g GHRH response was restored in the patients receiving substitutive therapy by HCG or testosterone . The alteration of GH response to GHRH in thalassaemic patients is likely to be only due to delayed puberty and decreased endogeneous GHRH secretion since it is corrected by androgen or gonadotropin replacement	Fair
11	Bronspiegel-Weintrob N, Olivieri NF, Tyler b, Andrews DF, Fredman MH, Holland FJ (1990) Effect of age at the start of iron chelation therapy on gonadal function in beta thalassaemia major N England J Medical 323(11), Sep , pp 71-9	Case control N= 40 patients	Beginning chelation treatment with desferrioxamine before the age of puberty can help children with transfusion-dependent thalassaemia major to attain normal sexual maturation	Poor
12	De Sanctis V, Vullo C, Katz M, Wonke B, Tanas R, Bagni B (1988) Gonadal Function in patients with beta thalassaemia major J Clin Pathol 41(2), Feb, pp 133-7	Case control study N= 23 patients	Patients had decreased gonadotropin reserves when compare with those of normal controls. Most of the thalassaemic patients with delayed puberty showed nomal gonad response to human menopausal gonadotrophi (hMG) but three had very low responses, when compared with that of controls	Poor

13	Borgna-Pignatti C, De Stefano P, Zonta L, Vullo C, De Sanctis V, Meleendi C, Naselli A, Masera G, Terzoli S, Gabutti V et al (1985) Growth and sexual maturation in thalassaemia major J Pediatric 106)1), Jan, pp 150-5	Cohort study N= 250 patients	37% of patients were found to be 2 SD below the mean for normal height, after age 14 years the percentage was 62% for males and 35% for females. 83% of males and 75% of females had delayed skeletal maturation. Complete lack of pubescent changes was present in 38% of females and 67% of males aged 12 to 18 years	Fair

PREVALENCE OF DIABETES MELLITUS IN THALASSAEMICS

No	Author, title Journal, year, volume, page	Study design, sample size, follow up	Outcome & Characteristic	Grade & comment
1	Chern JP, Lin KH, Lu MY, Lin DT, Lin KS, Chen JD, Fu CC (2001) Abnormal glucose tolerance in transfusion-dependent beta- thalassaemics patients Diabetes Care 24(5), May, pp 850-4	Cross sectional study N=89 patients	The prevalence of impaired glucose tolerance was 8.5% (7 of 82) and that of diabetes was 19.5% (16 of 82). The interaction of iron overload and hepatitis C infection worsened the prognosis of thalassaemic patients. Aggressive iron-chelation therapy as well as prevention and treatment o hepatitis C infection should be mandatory in managing glucose homeostasis in transfusion dependent beta thalassaemic patients	Poor
2	Telfer PT, Prestcott E, Holden S, Walker M, Hoffbrand AV, Wonke B (2000) Hepatic iron concentration combined with long term monitoring of serum ferrintin to predict complications of iron overload in thalassaemia major Br J Haemotol 110(4), Sep, pp 971-7	Cohort Study N= 32 patients	Most complications (eg cirrhosis, cardiomyopathy, diabetes etc) can be avoided if ferritin levels can be brought down to < 1500 microg/l	Fair
3	Gulati R, Bhatia V, Agarwal SS(2000) Early onset of endocrine abnormalities in beta-thalassaemia major in a developing country J Pediatric Endocrinol Metab. 13(6), Jun, pp 651-6	Cross sectional study N= 84 patients	Resukts showed 7.9% of patients with diabetes/impaired glucose tolerance. Thalassaemic patients in developing countries may be at risk for endocrine deficiencies at younger ages.	Poor
4	Labropoulou-Karatza C, Goritsas C, Fragopanagou H, Repandi M, Matsouka P, Alexandrides T (1999) High prevalence of diabetes mellitus among adult beta-thalassaemic patients with chronic hepatitis C	Cohort study	The frequency of diabetes in adult thalasaemia patients is significantly increased by HCV infection, even in the absence of cirrhosis. It is probable that the coexistence of haemochromatosis makes the effect of HCV infection on glucose metabolism clinically evident, even in the stage of chronic hepatitis	Fair

No	Author, title Journal, year, volume, page	Study design, sample size, follow up	Outcome & Characteristic	Grade & comment
	Eur J Gastoenterol Hepatol 11(9), Sep, pp 1033-6			
5	Borgna-Pignati c, Rugolotto S, De Stefano P, Piga A, Di Gregorio F, Gamberini MR, Sabato V, Melevendi C, Cappellini MD, Verlato G (1998) Survival and disease complications in thalassaemia mjor Ann N Y Acad Sci 30 (850) Jun, pp 227-31	Cohort Study N= 1146 F/up: 37 years	Diabetes was present in 5.4% of the patients	Fair
6	El-Hazmi MA, al-Swailem A, al-Fawaz I, Warsey AS, al-Swailem A (1994) Diabetes mellitus in children suffering from beta thalassaemia J Trop Pediatr 40(5), Oct, pp 261-6	Case-control study N= 100	The prevalence of diabetes is greatly improved if the serum ferrintin is kept below 2000 micrograms/I by regular chelation	Poor
7	Zupinger K, Molinari B, Hirt A, Imbach P, Gugler E, Tonz O, ZurbruggRP (1979) Increased risk o diabetes mellitus in beta thalassaemia major due to iron overload Helv Pediatr Acta 34(3):197-207	Cross-sectional study N= 22	Of 22 patients with beta-thalassaemia major (age 3-17 years) only 3 had a normal oral glucose tolerance	Poor

OSTEOPOROSIS IN THALASSAEMIA

No	Author, title, journal, year, volume, page	Study design, sample size, follow-up	Outcomes & characteristics	Comments
1	Chan YL. Pang LM. Chik KW. Cheng JC. Li CK. (2002) Patterns of bone diseases in transfusion-dependent homozygous thalassaemia major: predominance of osteoporosis and desferrioxamine-induced bone dysplasia. Pediatric Radiology, 32(7), July, pp 492-7	Cross-sectional N=41	41% with osteoporosis	Poor
2	Bielinski BK, Darbyshire P, Mathers L, Boivin CM, Shaw NJ (2001) Bone density in the Asian thalassaemic population: a cross-sectional review. Acta Paediatric, 90(11), Nov, pp 1262-6	Cohort study N = 11 pts	67% had osteoporosis	Fair the data confirm significant reductions in BMD in the Asian thalassaemic population, even after correcting for body size.
3	Lasco A, Morabito N, Gaudio A, Buemi M, Wasniewska M, Frisina N. (2001) Effects of hormonal replacement therapy on bone metabolism in young adults with beta-thalassemia major. Osteoporos Int; 12(7), pp 570-5	Non-randomised controlled prospective trial N = 40 patients	Osteoporosis observed at the lumbar level in treated patients, while in untreated patients it involves the femoral neck also.	4
4	Molyvda-Athanasopoulou E, Sioundas A,	Case-control	All patients had a significantly lower BMD	Poor

No	Author, title, journal, year, volume, page	Study design, sample size, follow-up	Outcomes & characteristics	Comments
	Karatzas N, Aggellaki M, Pazaitou K, Vainas I. (1999) Bone mineral density of patients with thalassemia major: four-year follow-up. Calcif Tissue Int, 4(6), Jun, pp 481-4	N= 50 F/up: 4 years	compared with healthy subjects.	
5	Lala R, Chiabotto P, Di Stefano M, Isaia GC, Garofalo F, Piga A.(1998) Bone density and metabolism in thalassaemia. J Pediatr Endocrinol Metab,11 (Suppl 3), pp 785-90	Clinical series N=: 27	Widespread bone alterations consisting of osteoporosis, growth failure and bone age delay.	Poor
6	Jensen CE, Tuck SM, Agnew JE, Koneru S, Morris RW, Yardumian A, Prescott E, Hoffbrand AV, Wonke B (1998) High prevalence of low bone mass in thalassaemia major. Br J Haematol, 103(4), Dec pp 911-5	Cohort study N=: 82 patients	51% of the patients had severely low bone mass and a further 45% had low bone mass.	Fair
7	Soliman AT. El Banna N. Abdel Fattah M. ElZalabani MM. Ansari BM. (1998) Bone mineral density in prepubertal children with beta-thalassemia: correlation with growth and hormonal data. Metabolism: Clinical & Experimental, 47(5), May, pp 541-8,	Case-control N= 30 pts	Children with beta-thalassemia had a significantly decreased bone mineral density and mean BMD% for age and sex.	Poor

No	Author, title, journal, year, volume, page	Study design, sample size, follow-up	Outcomes & characteristics	Comments
8	Anapliotou ML, Kastanias IT, Psara P, Evangelou EA, Liparaki M, Dimitriou P. (1995) The contribution of hypogonadism to the development of osteoporosis in thalassaemia major: new therapeutic approaches. Clin Endocrinol (Oxf), 42(3), Mar, pp 279-87	Cohort N= 67 patients Follow-up: 32 months	Spinal BMD was found to be more than 30% lower than that of controls matched for sex and age with no difference between sexes.	6
9	Katz K, Horev G, Goshen J, Tamary H.(1994) The pattern of bone disease in transfusion-dependent thalassemia major patients. Isr J Med Sci, 30(8), Aug, pp 577-80	Case series N=28 patients	39% had radiographic signs of osteoporosis, and 14% presented with fractures.	Poor
10	Giuzio E, Bria M, Bisconte MG, Caracciolo M, Misasi M, Nastro M, Brancati C. (1991) Skeletal changes in thalassemia major. Ital J Orthop Traumatol, 17(2), Jun, pp 269-75	Cohort study	Osteopenia (25%).	Fair
11	Canatan D, Akar N, Arcasoy A (1995) Effects of calcitonin therapy on osteoporosisi in patients with thalassemia Acta Haematologica, 93(1), pp 20-4	Non randomized controlled trial N=24 thalassemia major patients 14 received calcitonin plus calcium	After 1 year of treatment, bone pain disappeared and radiological sign of osteoporosis had improved significantly (p,0.01) in the treatment group. CT has no important role.	Good to fair

BLOOD TRANSFUSION

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size, Follow Up	Outcomes & Characteristics	Grade & Comment
1	U. Sprogoe-jakobsen, A.M. & ETRE, Georgsen J. (1995) Preparation of white cell-reduced red cells by filtration: comparison of a bedside filter and two blood bank filter systems Transfusion, 35, pp 421-426.	: 90 units of Buffy coat-depleted saline-adenine-glucose-mannitol (SAGM) RBCs were prepared. Thirty units were filtered with each of the two blood bank filter systems, and 30 units were filtered (but not, transfused) with the bedside filter in a clinical department after 8 to 24 days of storage.	Results: Four (13%) of the 30 units filtered at the bedside were filtration failures, compared to no failures with either of the blood bank filter systems. In addition, the median WBC content (0.14 x 106) of the units filtered at the bedside (2 units/filter) was significantly higher than that of the units filtered in the blood bank (0.05 x 101). The RBC loss was significantly higher with the filter systems than with the bedside filter, provided 2 units per filter were processed with the latter. The timed workload of. the filter systems was 45 to 75 minutes per 12 units, which was similar to the time required for bedside filtration.	
2	James J. Matthews RN. Holdsworth RF. Fulton A. Tauro GP. Hussein S. McGrath KM. (1986) The role of filtration in the provision of leukocyte poor red cells to multitransfused patients. Pathology 18(1), Jan, pp 127-30,	This study compare five methods of preparing leukocyte poor red cells with regards to their their efficiency in preventing febrile transfusion reactions with their cost of production, in order to establish a cost-effective transfusion programme for chronically anemic patients. 1. BCP (Buffy Coat Poor Red Cells) 2. MF (Microaggregate Filtered Red Cells) 3. CWF (Cotton Wool Filtered red cells) 4. WBCP (Washed Buffy Coat Poor Red Cells)	Leukocyte depletion and preparation costs per unit for the products were: microaggregate filtered red cells (MF): 25% leucocyte removal at a cost of $A2; buffy coat poor red cells (BCP): 70% at $A2; washed buffy coat poor red cells (WBCP): 88% at $A28, cotton wool filtered red cells (CWF): 93% at $A23; reconstituted frozen red cells (FC): 97% at $A80. The 5 products were transfused into 103 thalassemia patients with a documented history of febrile transfusion reactions. Reaction rates, expressed as a percentage of units transfused over a 12 mth period (MF 7%, BCP 0.3%, WBCP 0.1%, CWF 0.1%, FC 0.2%) correlated well with the degree of leukocyte depletion. The cost of CWF was reduced by a further 10% using the filter in line during the transfusion. There was no correlation between the antibodies present and the type of	Good to Fair

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		5. FC (Frozen Red Cells)	leukocyte poor product required by a patient to prevent a febrile reaction. A progressive regimen of transfusion (BCP to CWF to FC as the patient reacts) has now been adopted, with considerable cost saving.	
4	Sirchia G. Rebulla P. Parravicini A. Carnelli V. Gianotti GA. Bertolini F. (1987) Leukocyte depletion of red cell units at the bedside by transfusion through a new filter. Transfusion, 27(5), Sep-Oct, pp 402-5,.	Test done with a leukocyte removal filter (Sepacell R-500). During a 6-month period, 1550 PRC units were transfused through this filter in 611 transfusions to 80 multitransfused patients with thalassemia who had had a patient reaction rate (PRR) of 63 percent and a transfusion reaction rate (TRR) of 13 percent when given standard PRC or buffy-coat-depleted PRC.	When given filtered PRC, the PRR and TRR became 3.7 percent and 0.5 percent, respectively. By filtering 2 standard PRC units through the same filter, median values (and ranges) for red cell recovery and for residual leukocytes and platelets were 87 percent (83-92), 6.1 X 10^6 (0-100), and 2.7 X 10^9 (0.6-9.7), respectively. Refinements are needed to improve standardization of the filter and to increase red cell recovery (which is low when 1 unit is filtered through one filter) and blood administration rate,	poor
5	Ohene-Frempong K. Rappaport E. Schwartz E (1987.) Thalassemia syndromes. Recent advances. Hematology - Oncology Clinics of North America, 1(3), Sep, pp 503-19,.	Review	Supertransfusion (keeping HB > 12g/dl as been advocated but clinical value yet clearly established. The initial report suggesting that higher baseline hemoglobin could be maintained without increased transfusion requirement has not been the experience in treatment of some patients.Use of leukocyte-poor red cells preferable to minimize the incidence of febrile reactions. Practical value of neocytes not established in subsequent studies.	Poor
6	Tan KK, Lee WS, Liaw LC, Oh (1993) A prospective study on the use of leucocyte-filters	N= 26 patients (aged 9 months-13 years) F/up= 6-month period.	Transfusion reactions occurred in 8.5% (n = 18) of transfusions and in 42.3% (n = 11) of patients. 11.9% (n = 16) and 2.6% (n = 2) of reactions	Poor

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	in reducing blood transfusion reactions in multi-transfused thalassemic children. A.Singapore Med J, 34(2), Apr, pp 109-11	).	occurred in 50% (n = 9) and 25% (n = 2) of patients receiving buffy coat-poor PRC and filtered blood respectively. Transfusion reactions in toto were significantly reduced in the group receiving filtered blood ($p < 0.05$). However, febrile reaction alone was not significantly reduced ($p > 0.1$). The median onset and duration of reaction were 2 hours (range 10 minutes-18 hours) and 4 hours (range 1/2-24 hours) respectively. 72.2% (n = 13) of the reactions occurred occurred during transfusion. 88.8% (n = 16) of the reactions caused only one symptom. 19.2% (n = 5) of all patients had recurrent reactions, all of them receiving buffy coat-poor PRC. The commonest clinical manifestation was fever (n = 7), followed by urticaria (n = 5) and petechial rash (n = 2). The outcome was good, with no patient experiencing symptoms exceeding 24 hours. Only 0.9% (n = 2) of the transfusions were discontinued.	
7	Reverberi R, Menini C. (1190) Clinical efficacy of five filters specific for leukocyte removal. Vox Sang, 58(3), pp 188-91	Retrospective evaluation of the clinical efficacy of 5 filters specific for leukocyte depletion. Population was 191 thalassemics who received about 15,000 units of filtered blood in 28 months.	The frequencies of reactions to filtered blood varied significantly (p less than 0.0001) according to the type of filter and were as follows: Erypur, 0.7%; Imugard, 2.7%; Leucostop, 0.7%; Miropore, 2.1%; Sepacell, 0.6%. There was a notable concordance between the efficacy in the leukocyte removal and the clinical performance of the filters. The 2 polyester filters examined combined good clinical and laboratory results with superior flow properties.	poor
8	Rebulla P. (1990) Transfusion reactions in thalassemia. A survey	A survey on transfusion reactions in thalassemia was carried out within the COOLEYCARE	Reactions were reported in 1,225 of 111,590 red cell transfusions (1.1%) given during 40 months (September 1985-December 1987) to 3,755	Poor

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	from the Cooleycare programme. The Cooleycare Cooperative Group. Haematologica 75(Suppl 5), Sep-Oct, pp 122-7	Programme,	thalassemics in Italy and Greece. About 90% of red cell units were leukocyte-poor. Filtration was the most commonly used technique for leukocyte removal. Chills, fever, urticaria, headache and chest pain accounted for more than 80% of symptoms reported. Reactions were reported during transfusion in two thirds of cases. Although reactions were reported from 16% of patients, three quarters of reacting patients had no more than 2 reactions in 40 months.	
9	Propper RD, Button LN, Nathan DG. (1980) New approaches to the transfusion management of thalassemia. Blood 55(1), Jan, pp 55-60	Non-randomised controlled trial	Initially supertransfusion was accompanied by an initial increase in red cell requirement but after 1-4 months, all patients maintained hematocrit greater than 35% on a transfusion schedule identical to that of their previous standard transfusion regimen. Analysis of whole blood volumes of (12 out of 20) showed a mean reduction of 21% +/- 2%. The 2 patients on neocytes had the transfusion interval lengtheded form 30 +/- 2.5 days to 43 +/- 4.5 days.	Fair
10	Cohen AR. Schmidt JM. Martin MB. Barnsley W. Schwartz E. (1984) Clinical trial of young red cell transfusions. Journal of Pediatrics, 104(6), Jun, pp 865-8	Prospective Study.	The mean transfusion requirement to maintain the hemoglobin level greater than 9.0 gm/dl was 110 +/- 17 ml RBC/kg during the year of young cell transfusions, in comparison with 130 +/- 20 and 131 +/- 23 ml RBC/kg when conventional frozen cells were administered in the years before and after the young cell trial, respectively. Blood requirements in individual patients were reduced by 8% to 24% (mean 15.8%); the hemoglobin level remained constant. The cost for comparable amounts of red cells is	Poor

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			$134.80 (2 x $67.40) for young red cells using freezing techniques and $61.70 for normal frozen blood. Although young cells of consistent quality can be prepared regularly in a clinical setting with little difficulty, the cost of the product is high and the effect on transfusion requirements is less than predicted from studies in vitro and from labeling experiments.	
11	Marcus RE. Wonke B. Bantock HM. Thomas MJ. Parry ES. Taite H. Huehns ER. (1985) A prospective trial of young red cells in 48 patients with transfusion-dependent thalassaemia. British Journal of Haematology, 60(1), May, pp 153-9	Prospective Randomised Controlled Trial. N= 52 Patients F/ up: 1 year.	No difference seen between the 2 groups with respect to transfusion interval, mean Hb and rate of Hb fall.Conclusion: any reduction in the rate of iron loading brought about by the use of YRBC is clinically insignificant and does not justify the expense, time and work required to produce young red cells for use in a large transfusion dependent thalassaemic population.Filtered blood was shown to be as effective as frozen blood in eliminating non-haemolytic febrile transfusion reactions in all the trial patients.	Good
12	Spanos T. Ladis V. Palamidou F. Papassotiriou I. Banagi A. Premetis E. Kattamis C (1996) The impact of neocyte transfusion in the management of thalassaemia. Vox Sanguinis, 70(4), pp 217-23	Case study N=18 patients.	The total annually transfused red blood cells and concomitant iron blood load were significantly reduced ($p < 0.001$) by 20.2 +/- 9.1%. However, the response was variable. Seven of the 18 patients had a large reduction in blood consumption (24.8-34.8%), 9 others ranged between 10.7 and 21.6%, and in 2 the reduction was less than 10%.	Poor
13	Kevy SV. Jacobson MS. Fosburrg M. Renaud M. Scanlon A. Carmen R. Nelson E. (1991)		Thalassemic patients receiving neocytes had an average decrease of 21.1% in red cells per kg/yr as compared to their frozen red cell requirement, and	

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	[A new approach for transfusion of neocytes: the Neocel system]. Revue Francaise de Transfusion et d Hemobiologie, 34(3), May, pp249-55		an average of 6.9% fewer transfusions.	
14	Bertholey F. Saint-Paul E. Chataing B. Clerc M. Bertrand Y. Souillet G. Philippe N. (1990) [Transfusion of concentrates enriched in neocytes in the thalassemic child. Preliminary results]. Revue Francaise de Transfusion et d Hemobiologie, 33(3), Jun, pp 165-74,	Case study Only 3 thalasaemic children . Compared the results of young red cells transfusion for 12 months with the administration of conventional red cells units during the year before.	The mean decrease of hemoglobin transfused per kg of body weight per year was 22%. The mean pretransfusion hemoglobin level did not change during the 2 years of study.	Poor Only.Small number of subjects
15	Kevy SV. Jacobson MS. Fosburg M. Renaud M. Scanlon A. Carmen R. Nelson E. (1988) A new approach to neocyte transfusion: preliminary report. Journal of Clinical Apheresis 4, pp194-7		Based on a 12 month period, the patients as a group have received an average of 14% fewer transfusions and an 18% decrease in red cells per kg/yr as compared to frozen red cells.	Abstract Only
16	Michail-Merianou V. Pamphili-Panousopoulou L. Piperi-Lowes L. Pelegrinis E. Karaklis A. (1987) Alloimmunization to red cell antigens in thalassemia: comparative study of usual versus better-match transfusion programmes. Vox Sanguinis, 52(1-2), pp 95-8,	Prospective comparative study N=120 regularly transfused thal children. -64 (31 girls , 33 boys) received UM blood. 56 (20 girls and 36 boys) received BM blood F/up: March 1980 to March 1985.	A statistically significant difference does not exist in the overall frequency of alloimmunization between the UM (23.43%) and BM group (14.28%) and also between the children that started transfusion therapy before they were 12 months old regarding UM (9%) and BM policies (5.2%). However, a large numerical difference, which might become statistically significant with a larger number of patients was observed in the group of children who were started on transfusions after they were 12 months old, between the UM (38.7%) and	Good

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		.	BM (18.9%) policy. Finally, a statistically significant difference (less than 0.005) was found only between the children that started transfusions early (7.69%) and those that started them later in life (27.9%), irrespective of the transfusion policy observed.	
17	Rebulla P. Modell B.(1991) Transfusion requirements and effects in patients with thalassaemia major. Cooleycare Programme. Lancet, 337(8736), Feb 2, pp 277-80,	Review It an analysis of data available in 1985 on 3468 Italian and Greek patients registered in Cooleycare, an international cooperative programme of quality assessment of treatment delivery in thalassaemia, gave the following picture of treatment requirements and effects.	The proportion of patients undergoing splenectomy has progressively decreased, and age at splenectomy has increased with time over the past 20 years. Age at first transfusion exceeds 4 years in a small but important group of patients, which indicates that a milder form of thalassaemia exists in this group. Children receiving modern treatment remain of near-normal stature until age 11 but later tend to be stunted. The mean blood requirement is 35% higher in non-splenectomised than in splenectomised patients. Differences in transfusion interval of 2 to 4 weeks have no measurable effect on blood requirement. Mean blood requirement rises gradually with mean haemoglobin concentration, possibly in a non-linear fashion. The prevalence of red cell alloimmunisation rises with delay in start on transfusion. Transfusion reactions were reported in 1% of transfusions (90% of which were leucocyte-depleted), from 17% of patients.	Poor
18	Spanos T, Karageorga M, Ladis V, Peristeri J, Hatziliami A, Kattamis C. (1990)	Prospective study	Of 1,038 patients who received blood only matched for AB0 and Rh-D 244 (23.5%) with one or more	Good to Fair

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	Red cell alloantibodies in patients with thalassemia. Vox Sang, 58(1), pp50-5	N=1200 patients (607 males and 593 females) F/ up: 1981-1987.	red cell alloantibodies were identified. Of these 1,038 patients, 973 were exclusively thalassemic. In 220 (22.6%) of them, alloantibodies were found. (21.1% clinically significant antibodies) In 162 patients who received blood matched for the AB0, rhesus and Kell systems from their first transfusion, the immunization rate was very low (3.7%). In a pilot group consisting of 83 patients with the same clinical characteristics, who received blood matched only for the AB0 and Rh-D antigens, there was a significant difference in the frequency of alloantibodies (15.7%, p less than 0.001).The sickle cell beta-thalassemia patients presented alloantibodies with a higher frequency (36.9%, 24/65).Only one antibody was found in 114 patients (51.8%) and two or more in 106 patients (48.2%).The alloimmunization significantly concerned the rhesus (34.0%) and Kell (29.8%) systems. Anti-Kell was most often identified (28.5%). Alloimmunization appears considerably lower in patients in whom blood transfusion is started before the age of 3 than in those in whom it is started after that age (20.9 vs. 47.5%, p less than 0.0001).	
19	Singer ST. Wu V. Mignacca R. Kuypers FA. Morel P. Vichinsky EP. (2000) Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly asian descent. Blood, 96(10), Nov 15, 3369-73	Clinical and transfusion records of 64 (75% Asian) thalassaemia patients (mean age, 15 years; range 2 – 39) who received regular transfusion were analyzed. The frequency, causes and prevention of the development of hemolytic alloantibodies and	14 (22%) of 64 patients (75% Asian) became alloimmunized. A mismatched RBC phenotype between the white population, comprising the majority of the donor pool, and that of the Asian recipients, was found for K, c, S, and Fyb antigens, which accounts for 38% of the alloantibodies among Asian patients. Patients who had a splenectomy had a higher rate of alloimmunization than patients who did not have a splenectomy (36%	Poor

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		erythrocyte autoantibodies were evaluated. The effect of red blood cell (RBC) phenotypic differences between donors (mostly white) and Asian recipients on the frequency of alloimmunization was determined. Additional transfusion and patient immune factors were examined.	vs 12.8%; P =.06). Erythrocyte autoantibodies, as determined by a positive Coombs test, developed in 25% or 16 of the 64 patients, thereby causing severe hemolytic anemia in 3 of 16 patients.Of these 16, 11 antibodies were typed immunoglobulin G [IgG], and 5 were typed IgM. Autoimmunization was associated with alloimmunization and with the absence of spleen (44% and 56%, respectively). Transfusion of phenotypically matched blood for the Rh and Kell (leukodepleted in 92%) systems compared to blood phenotypically matched for the standard ABO-D system (leukodepleted in 60%) proved to be effective in preventing alloimmunization (2.8% vs 33%; P =.0005).	
20	Fongsatitkul L. Bannawat U. Sanguansermsri T. Kulapongs P. Unexpected red cell antibodies in thalassemic children. Birth Defects: Original Article Series1988;. 23(5B):291-3	632 thalassaemic children were evaluated for alloantibodies after repeated transfusion.	Nineteen of the 632 (3%) children with homozygous beta-thal and beta thal/Hb E developed alloantibodies to red cell antigens, There were eight cases of anti-E, four cases of anti-E+, and two cases of anti-Le(a + b) antibodies..	Abstract Only
21	Tardtong P. Ratanasirivanich P. Chiewsilp P. Hathirat P. (1988) Red cell antibodies in thalassemia hemoglobinopathy patients. Birth Defects: Original Article Series, 23(5B), pp287-9	N=164 patients	Immunization to red blood cell occurred in 14 patients (8.5%). Among these, 11 patients had alloantibody, one patient had autoimmune antibody, and two patients had both alloantibody and autoimmune antibody. The naturally occurring antibody (anti-Leb) was observed in pretransfused blood samples of two patients (1.2%). Most red cell immunization seemed to occur in the early period of blood transfusion	Poor

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22	Hmida S, Mojaat N, Maamar M, Bejaoui M, Mediouni M, Boukef K. (1994) Red cell alloantibodies in patients with haemoglobinopathies. Nouv Rev Fr Hematol,36(5), Oct, pp 363-6	N= 364 patients -127 were thalassemic and 182 had sickle cell disease (SCD). F/up:1990-1993).	In 55 control patients, who received blood matched for the ABO, Rhesus and Kell antigen systems from the outset of transfusion, no immunization was detected. However, in the study group, who initially received blood matched only for ABH and Rh D antigens, the frequency of alloimmunization was 7.76% (24/309). Only one antibody was detected in 15 patients (62.5%) and two or more in 9 patients (37.5%). Alloimmunization concerned the Rhesus system in 58.82% of cases and the Kell system in 26.47%, while the frequency of immunization was significantly lower in patients of less than 5 years as compared to those in the age range 5-10 years ($p < 0.001$).	Poor
23	Kattamis C, TouliaKattamis C. Touliatos N. Haidas S. Matsaniotis N. (1970) Growth of children with thalassaemia: effect of different transfusion regimens. Archives of Disease in Childhood, 45(242), Aug, pp502-9	Retrospective study. N= 74 children with thal major (39 boys and 35 girls).	Children in group l grew normally both in weigh and height, those in groups ll and lll were retarded especially Group lll.	Poor

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24	Propper RD, Button LN, Nathan DG. (1980) New approaches to the transfusion management of thalassemia. Blood, 55(1),:Jan, pp 55-60	N= 20 splenectomised thalassaemic patients on chronic subcutaneous desferrioxamine, aged 5 – 25 yr. Not randomized. On standard transfusion regime, all patients received washed, frozen packed cells every 4-5 wk to maintain hematocrits greater than 27% for (?) 1 year. Then they were shifted to supertransfusion to maintain the hematocrit > 35%. They also described the use of neocytes on 2 patients.	Initially supertransfusion was accompanied by an initial increase in red cell requirement but after 1-4 months, all patients maintained hematocrit greater than 35% on a transfusion schedule identical to that of their previous standard transfusion regimen. Analysis of whole blood volumes of (12 out of 20) showed a mean reduction of 21% +/- 2%. The 2 patients on neocytes had the transfusion interval lengtheded form 30 +/- 2.5 days to 43 +/- 4.5 days.	Fair
25	Masera G. Terzoli S. Avanzini A. Fontanelli G. Mauri RA. Piacentini G. Ferrari M. (1982) Evaluation of the supertransfusion regimen in homozygous beta-thalassaemia children. British Journal of Haematology, 52(1), pp111-3	11 splenectomised, homozygous beta-thal aged 6 – 14 years. All receiving desferral (40 mg/kg/day). Monthly blood consumption was measured during standard transfusion regimen (mean pre-transfusion Hb 10.2 g/dl) for 4-12 months then compared with a second period of supertransfusion regimen (mean pre-transfusion Hb 12.3 g/dl) for 7-18 months.	Blood consumption was 16.71 +/- 2.0 ml/kg/month in the first period; it rose to 20.30 +/- 3.5 ml/kg/month in the first 5 months of the second period, and then returned to the values of the first period (16.53 +/0 2.0 ml/kg/month). There were no significant differences in blood consumption between the two transfusion regimens, after the 5-month equilibration period.	Poor

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26	Ohene-Frempong K. Rappaport E. Schwartz E. (1987) Thalassemia syndromes. Recent advances. Hematology - Oncology Clinics of North America,1(3), pp 503-19,	Review	Supertransfusion (keeping HB > 12g/dl as been advocated but clinical value yet clearly established. The initial report suggesting that higher baseline hemoglobin could be maintained without increased transfusion requirement has not been the experience in treatment of some patients. Use of leukocyte-poor red cells preferable to minimize the incidence of febrile reactions. Practical value of neocytes not established in subsequent studies.	Poor
27	Piomelli S. Loew T. (1991) Management of thalassemia major (Cooley's anemia). Hematology - Oncology Clinics of North America, 5(3), Jun, pp 557-69	Review .	Type of Blood Product: Filtered blood to remove leukocutes. Frequency of Transfusion. 2- 3 weekly. 50% more blood is required to transfuse every 6 weeks then every 3 weeks. Baseline Hb Level: keeps Hb at least 10 – 10.5. g/dL. or higher.	Poor.
28	De Sanctis V, Katz M, Vullo C, Bagni B, Ughi M, Wonke B. (1994) Effect of different treatment regimes on linear growth and final height in beta-thalassaemia major. Clin Endocrinol (Oxf), 40(6),:Jun, pp 791-8	Retrospective Study N= 64 patients (28 males and 36 females). subcutaneous chelation therapy very early, at a mean age of 2 years.	These data suggest that an ideal therapeutic regime has yet to be found which avoids the toxic effect of iron overload and on the other hand avoids interference with growth, secondary to desferrioxamine.	Poor
29	Cazzola M, De Stefano P, Ponchio L, Locatelli F, Beguin Y, Dessi C, Barella S, Cao A, Galanello R. (1995) Relationship between transfusion regimen and suppression of erythropoiesis in beta-thalassaemia major.	Actually 2 studies. 1. To confirm that serum transferring receptor level is a specific marker of effective suppression of	As measured through serum transferrin receptor, erythroid activity was 1-2 times normal for pretransfusion haemoglobin levels between 10 and 11 g/dl.1-4 times normal for levels from 9 to 10 g/dl, (b Thal trait have erythroid activity of 1-3 times normal)2-6 times normal for levels from 8.6 to 9 g/dl. Mean pretransfusion haemoglobin was	

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	Br J Haematol, 89(3), May, pp:473-8	erythropoiesis. 2. To the apply this to 52 patients with beta thal major whose mean pretransfusion haemoglobin levels ranged from 8.6 to 10.9 g/dl. To look into the level of suppression of erythropoiesis with different regimens. .	also inversely related to serum erythropoietin (r = -0.72, P < 0.001), whereas it showed no or a weak relationship with Hb F, reticulocyte count, or circulating nucleated red cell count. Therefore, pretransfusion haemoglobin values of < or = 9 g/dl should be adopted with caution, because these levels can be associated with an insufficient inhibition of erythroid marrow expansion. However, a transfusion programme, with a baseline haemoglobin of 9-10 g/dl, may provide enough suppression of erythropoiesis and allow a reduction in blood consumption as compared with the classic hyper- or supertransfusion schemes.	
30	Cazzola M. Borgna-Pignatti C. Locatelli F. Ponchio L. Beguin Y. De Stefano P. (1997) A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis. Transfusion, 37(2), Feb, pp 35-40	Prospective study. N=32 patients F/up: mid 1981 to 1986 From 1987 to 1992 they were changed to a moderate transfusion regime. (pretransfusion hemoglobin of 9.4 +/- 0.4 g per dL). Compliance to chelation did not differ significantly in the 2 periods of study. The degree of erythroid marrow activity was compared between these patients and in 32 (controls) subjects with beta-thalassemia intermedia through the simple measurement of serum	After the adoption of the moderate transfusion regimen, transfusion requirements decreased from 137 +/- 26 to 104 +/- 23 mL per kg per year of red cells (p < 0.0001), Saving in transfusion iron averaging 40 mg/kg/year per patient.Mean serum ferritin decreased from 2448 +/- 1515 to 1187 +/- 816 micrograms per L (p < 0.0001), with one-half of patients achieving serum ferritin levels lower than 1000 micrograms per L. The proportion of patients having spontaneous pubertal development increased significantly (p < 0.01), as a result of less iron-related gonadotropin insufficiency. At the lower pretransfusion hemoglobin, erythroid marrow activity did not exceed two to three times normal levels in most subjects. (And was lower than erythroid morrow activity in the intermedia group p<0.0001).CONCLUSION: As compared with hypertransfusion, moderate transfusion may allow more effective prevention of iron loading, with higher likelihood of spontaneous pubertal	Fair

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		transferrin receptor.	development and without producing excessive expansion of erythropoiesis.	
31	Prati D. (2000) Benefits and complications of regular blood transfusion in patients with beta-thalassaemia major. Vox Sanguinis, 79(3), pp 129-37	Review.	Pre-transfusion haemoglobin concentration should not exceed 95 g/l and this allows adequate control of anaemia, with a relatively low rate of iron accumulation.	Poor
32	Albo C. Cabrera J. Dios A. Castro M. Ares C. Constenla I. Lopez D. (1995) [Program of hypertransfusion and chelation with desferrioxamine in 10 patients with thalassemia major]. Sangre, 40(6), Dec, pp 441-5,.	N= 10 patients F/up: 11 years	Two patients died of heart iron overload. The mean ferritin values at the end of the study were around 3.031 mg/mL. Cardiac dysfunction occurred in 2 cases2 patients had retarded growth, decreased IGF-1 being found in both; 3 cases had hypogonadotropic hypogonadism, and 2 had clinical hypoparathyroidism. Bilateral opacification of the eye lens appeared in one patients as a consequence of prolonged DFO therapy. Positive IAT was found in 3 cases, and one patient developed positive hepatitis C serology.	Poor
33	Ginsberg G. Tulchinsky T. Filon D. Goldfarb A. Abramov L. Rachmilevitz EA.Cost-benefit analysis of a national thalassaemia prevention programme in Israel. Journal of Medical Screening. 5(3):120-6, 1998	N= 200 known living subjects with **thalassaemia** major,	The lifetime healthcare costs of caring for a person born with thalassaemia major are $284,154. The costs of the home infusion service (33.1%) actually exceed the costs of the chelating agent itself (22.1%). The remaining 44.8% of costs are due to stay in hospital, operations, outpatient visits, laboratory tests, therapists, etc. Lost earnings and premature mortality costs account for a further $51,843 and $141,944 respectively for each case. A national screening programme would cost $900,197 and prevent around 13.4 homozygotes being born, at a cost of $67,369 for each birth	Poor

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			prevented. The benefit-cost ratio of the programme to the health services is 4.22:1, which increases to 6.01:1 when a societal perspective is taken. However, around 13.0 homozygote births are still expected to occur, the majority owing to lack of compliance of patients at various stages in the screening process. The addition of a national health education programme for the higher risk non-Jewish population either nationally or in selected regions will incur extra costs, which may be covered by increased benefits as a result of better compliance with the screening programme.	

DESFERRIOXAMINE

No	Author , Title, Journal, Year, Vol, Page No	Study design, Sample Size,Follow up	Outcomes and characteristics	Grade & Comment
1	Olivieri NF, Koren G, Harris J, Khattak S, Freedman MH, Templeton DM, Bailey JD, Reilly BJ. (1992) Growth failure and bony changes induced by desferrioxamine. Am J Pediatr Hematol Oncol, 14(1), pp 48-56	Comparative study	Only patients begun on desferrioxamine prior to age 2 years demonstrated a significant (p less than 0.01) decline in height percentile by the third year, implicating desferrioxamine therapy as the cause of growth failure. Conclusion: that both the decline in height percentile and the bony changes observed in well-chelated patients are directly related to desferrioxamine therapy.	Poor
2	Wang C, Tso SC, Todd D (1989) -Hypogonadotropic hypogonadism in severe beta-thalassemia: effect of chelation and pulsatile gonadotropin-releasing hormone therapy	Case study	Conclusion: chronic iron overload in patients with severe thalassemia leads to variable degrees of hypogonadotropic hypogonadism, which do not respond to chelation therapy given late in the course of the disease. The hypogonadism in most patients	Poor

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	J of Clinical Endo & Metab, 68, pp 511-516		was due to pituitary hyporesponsiveness to GnRH.	
3	Cohen AR, Mizanin J, Schwartz E. (1990) Rapid removal of excessive iron with daily, high-dose intravenous chelation therapy. J.Pediatr, 116(1), Jan, pp 157-8	Case study	•Sr ferritin levels decreased by 56% to 99%. Liver iron concentrations, measured by magnetic susceptibility in two patients, were 1234 and 2438 micrograms/gm wet weight (22.1 and 43.6 mumol/gm wet weight) after treatment for 17 and 25 months, respectively. A patient with congestive heart failure and a patient with severe ventricular dysrhythmias no longer required cardiac medication after 12 to 24 months of chelation therapy.	Poor
4	Di Gregorio F, Romeo MA, Pizzarelli G, Aiello G, Russo G. (1997) An alternative to continuous subcutaneous infusion of desferrioxamine in thalassaemic patients. Br J Haematol, 98(3), Sep, pp 601-2	Case study	The two methods of DF administration produced no significant differences in urinary iron excretion. No significant changes in serum ferritin levels were observed at the end of the study. Compared with continuous infusion, rapid injection is equally efficacious, does not induce serious side-effects, is better accepted by the patients, and can improve their compliance to the iron-chelating therapy.	Poor
5	Khuzaiah R , Shekar K Comprehensive care of transfusion dependent thalassemia: Projection of cost requirements Paper work submitted to Ministry of health Malaysia	Determine the cost of chelation therapy in transfusion dependent thalassemia (TDT) patients and projected total and incremental cost outlays,in the setting of a 100 patient thalassemic clinic.The projected TDT population can was calculated fr the case base scenario available	The cost effectiveness ratio of 20 year chelation programme is RM 1500/QALY (quality adjusted life year gained) saved. Conclusion:the initiation of chelation therapy in transfusion dependent Thalassemia patients is undoubtedly, a cost effective intervention. Futher,to maximize the cost effectiveness of such an intervention,it is necessary that chelation be commenced early (less than 10 years of age)	8

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		at thalassemia clinic,survival data were literature derived.		
6	Caro JJ, Ward A, Green TC, Huybrechts K, Arana A, Wait S, Eleftheriou A. (2002) Impact of thalassemia major on patients and their families. Acta Haematol, 107(3), pp 150-7	Survey F/up:October 1999 to May 2000	1,888 questionnaires (65%) were returned. The responses suggest that nowadays patients begin blood transfusions, and most use desferrioxamine (84.8%), but iron-related complications, including life-threatening ones such as heart disease, are still common. CONCLUSIONS: There remains a need to improve the management of thalassemia, as many patients with iron-related complications experience physical and social limitations	Poor
7	Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, Allen CJ, Farrell DE, Harris JW. Efficacy of desferrioxamine in preventing complications of iron overload in patients with thalassemia major. N Engl J Med 1994 Sep 1;331(9):567-73	N= 59 F/up: 4 to 10 year or until death	The body iron burden as assessed by magnetic measurement of hepatic iron stores was closely correlated ($R = 0.89$, $P < 0.001$) with the ratio of cumulative transfusional iron load to cumulative desferrioxamine use (expressed in millimoles of iron per kilogram of body weight, in relation to grams of desferrioxamine per kilogram, transformed into the natural logarithm). Each increase of one unit in the natural logarithm of the ratio (transfusional iron load to desferrioxamine use) was associated with an increased risk of impaired glucose tolerance (relative risk, 19.3; 95 percent confidence interval, 4.8 to 77.4), diabetes mellitus (relative risk, 9.2; 95 percent confidence interval, 1.8 to 47.7), cardiac disease (relative risk, 9.9; 95 percent confidence interval, 1.9 to 51.2), and death (relative risk, 12.6; 95 percent confidence interval, 2.4 to 65.4). All nine deaths during the study occurred among the 23 patients who had begun chelation therapy later and used less desferrioxamine in relation to their transfusional iron load ($P < 0.001$). CONCLUSIONS. The early	

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			use of desferrioxamine in an amount proportional to the transfusional iron load reduces the body iron burden and helps protect against diabetes mellitus, cardiac disease, and early death in patients with thalassemia major.	
8	Porter JB, Jaswon MS, Huehns ER, East CA, Hazell JW (1989) Desferrioxamine ototoxicity: evaluation of risk factors in thalassaemic patients and guidelines for safe dosage. Br J Haematol,173(3), Nov, pp 403-9.	Cross sectional N=Forty-seven patients	The two most significant risk factors were the maximum dose of DFO previously received (P less than 0.01), and a serum ferritin of less than 2000 micrograms/l at that time (P less than 0.001). A therapeutic index obtained from the ratio of the mean daily dose of DFO mg/kg divided by the serum ferritin identifies patients with a ratio of greater than 0.025 as at risk of sensorineural hearing loss (P less than 0.001) and can be used as a guideline for safe DFO dosage. Follow-up audiometry of the affected patients over a 2-year period indicated that adjustment of the dose to a therapeutic index of less than 0.025 resulted in the stabilization of hearing loss in seven patients and improvement in two.	Poor
9	Davies SC , Marcus RE, Hungerford JL, Miller MH, Arden G, Huehns ER (1983) Ocular toxicity of high-dose intravenous desferrioxamine. Lancet, 2(8343), July 23, pp 181-4.	Case reports N=four patients.	In two of them retinal abnormalities developed, presenting with night blindness and field defects, which improved on withdrawal of the drug	Poor
10	Orton RB, de Veber LL, Sulh HM (1985) Ocular and auditory toxicity of long-term, high-dose subcutaneous desferrioxamine therapy.	Case reports N= two siblings	Both had visual loss secondary to optic neuropathy and sensorineural hearing loss. After discontinuation of the drug one sibling showed almost complete reversal of the optic neuropathy,	Poor

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	Can J Ophthalmol, 20(4), Jun 1, pp 153-6.		but the other had a permanent unilateral visual loss. Both had a permanent hearing loss but benefited from hearing aids. The mechanism of these complications is presently unknown. Patients receiving desferrioxamine should be closely monitored for ocular and auditory side effects. When such effects are detected the drug should be discontinued and the patient observed for improvement. When improvement has stabilized, therapy should be restarted at a reduced dosage.	
11	Koren G, Bentur, Y Strong D, Harvey E, Klein J, Baumal R, Spielberg SP ; Freedman MH (1989) Acute changes in renal function associated with desferrioxamine therapy. Am J Dis Child, 143(9), Sept 1, pp 1077-80.	Case reports N= three patients	there was a twofold to eightfold increase in plasma creatinine level and a parallel decrease in creatinine clearance that resolved when treatment with the drug was discontinued. Desferrioxamine induced an acute increase in the fractional excretion of sodium, potassium, chloride, phosphate, and urate but did not affect the glomerular filtration rate and renal blood flow.	9
12	Freedman MH, Grisaru D, Olivieri N, MacLusky I, Thorner PS (1990) Pulmonary syndrome in patients with thalassemia major receiving intravenous desferrioxamine infusions. Am J Dis Child, 144(5), May 1, pp 565-9.	Cross sectional N=Eight patients	four patients developed a pulmonary syndrome of moderate to life-threatening severity. Pulmonary function studies showed restrictive dysfunction. Lung biopsy showed diffuse abnormalities with alveolar damage, interstitial fibrosis, and inflammation.. Detailed studies failed to identify an infectious agent. The temporal relationship between drug administration and lung disease, and the clinical similarities in the four affected patients, strongly suggested a cause and effect relationship.	8
13	Brill PW, Winchester P, Giardina PJ ; Cunningham-Rundles S (1991) Desferrioxamine-induced bone dysplasia in	Case control studies N=25, -3,desferral started before 3 yrs ,22,desferral started after 3	Metaphyseal irregularity and abnormal vertebral bodies resembling a bone dysplasia were seen in two of five children with thalassemia major who were begun on a regimen of hypertransfusion and	Poor

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	patients with thalassemia major American Journal of Roentgenology, 156, pp 561-565	yrs	chelation with desferrioxamine before the age of 3 years. Similar changes were not seen in 22 other children in whom chelation was started after the age of 3. Whether the dysplastic bone growth was related to drug dose or age of onset of chelation could not be determined, as desferrioxamine dosages differed in the two groups	
14	Orzincolo C, Scutellari PN, Castaldi G (1992) Growth plate injury of the long bones in treated beta-thalassemia. Skeletal Radiol, 21(1), Jan 1, pp 39-4 .	Cross sectional N=12 patients	radiologic abnormalities of the long bones were observed similar to those observed in rickets and scurvy. These abnormalities were associated with a growth retardation. The pathogenesis of these lesions is uncertain, but probably the toxic effect of desferrioxamine plays an important role in their development. A relative deficiency of vitamins D and/or C cannot be entirely excluded	Poor
15	Hartkamp MJ, Babyn PS, Olivieri F (1993) Spinal deformities in desferrioxamine-treated homozygous beta-thalassemia major patients. Pediatr Radiol, 23(7), Jan 1, pp 525-8.	Retrospective study N= 22 HBT patients who were receiving DF therapy,	(decreased spinal height, increased thoracic kyphosis, vertebral flattening and elongation anteriorly, and disk calcification) were found in 16 of 22 patients. These changes are believed to be caused by interference with spinal growth-plate development. Investigation of DF-dose correlation supports the conclusion that the spinal changes were DF-induced. Spinal changes observed in DF-treated patients differ both morphologically and pathogenetically from earlier reports of vertebral deformities morphological deformities occurring as a sequel to compensatory marrow hyperplasia in poorly transfused patients.	Poor
16	Modell B, Letsky EA, Flynn DM, Peto R, Weatherall DJ. (1982)• Survival and desferrioxamine in thalassaemia major	Randomised trial and observation	those patients who had received average weekly doses of more than 4 g of desferrioxamine over the previous few years were less likely to die in the near future than were patients of similar ages who had	good Small sample

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	Br Med J (Clin Res Ed) , 284(6322), Apr 10, pp 1081-4		received less, or no, desferrioxamine.	
17	Freeman AP, Giles RW, Berdoukas VA, Walsh WF, Choy D, Murray PC. (1983)• Early left ventricular dysfunction and chelation therapy in thalassemia major. Ann Intern Med,99(4), Oct, pp450-4	N= 23 asymptomatic patients with thalassemia major.	12 of the twenty-three patients were receiving chelation therapy with subcutaneous desferrioxamine. Ejection fraction at rest was normal in 11 of these patients. During exercise a normal ventricular response was shown in 4 patients. After 1 year of intensive chelation therapy in these 12 patients, left ventricular function was reassessed. A normal exercise response was seen in an additional 4 patients;	Poor
18	Wolfe L, Olivieri N, Sallan D, Colan S, Rose V, Propper R, Freedman MH, Nathan DG (1985)• Prevention of cardiac disease by subcutaneous desferrioxamine in patients with thalassemia major the efficacy of long-term NEMJ, 25(312), June 20, pp 1600-1603	Subcutaneous desferrioxamine therapy in the prevention of iron-related cardiac disease in patients with thalassemia major who began treatment after the age of 10 years were examined.	• 36 pts without preexisting cardiac disease, 19 did not comply with the program of chelation therapy. Over the course of Rx (1977 to 1983) sr ferritin and ALT levels fell in the compliant gp, fr mean values (+/- S.D.) of 4765 +/- 2610 to 2950 +/- 1850 ng /ml and 58.1 +/- 22 IU to 30 +/- 20 IU/l, respectively (P less than 0.05), but rose in the noncompliant gp, from 5000 +/- 2316 to 6040 +/- 2550 ng /ml and 56.6 +/- 20 to 90 +/- 35 IU /l, respectively.. In contrast, 12 noncompliant patients acquired cardiac disease, and 7 died.	Poor
19	Aldouri MA, Wonke B, Hoffbrand AV, Flynn DM, Ward SE, (1990) High incidence of cardiomyopathy in beta-thalassaemia patients receiving regular transfusion and iron chelation: reversal by intensified chelation.	Cardiac scintigraphy has been performed in 60 beta-thalassaemia major patients aged 8-35 years who received regular blood transfusions and subcutaneous desferrioxamine (DFX) chelation.	Non-compliant patients (defined as the use of subcutaneous DFX less than 4 times weekly) generally showed worse cardiac function. Repeat study on 17 patients after 6-28 months of better compliance with subcutaneous or intravenous DFX (using an indwelling catheter) showed a significant overall improvement in LVEF associated with a significant drop in serum ferritin.	Poor

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	Acta Haematol, 84(3), pp 113-7			
20	Nancy F. Olivieri, David G. Nathan, James H. MacMillan, Alan S. Wayne, Peter P. Liu, Allison McGee, Marie Martin, Gideon Koren, and Alan R. Cohen (1994)•. Survival in Medically Treated Patients with Homozygous ß-Thalassemia NEMJ, 331(9), Sept 1, pp574-578	97 patients born before 1976 who were treated with regular transfusions and chelation therapy were studied.	Of the 97 patients, 59 (61 percent) had no cardiac disease; 36 (37 percent) had cardiac disease, and 18 of them had died. factors affecting cardiac disease-free survival were -age at the start of chelation therapy, -the serum ferritin concentration before chelation therapy began -the proportion of ferritin measurements exceeding 2500 ng per milliliter -Patients in whom less than 33 percent of the serum ferritin values exceeded 2500 ng per milliliter had estimated rates of survival without cardiac disease of 100 percent after 10 years of chelation therapy and 91 percent after 15 years.	Poor
21	Gary M. Brittenham, Patricia M. Griffith, Arthur W. Nienhuis, Christine E. McLaren, Neal S. Young, Eben E. Tucker, Christopher J. Allen, David E. Farrell, and John W. Harris (1995)• Efficacy of Desferrioxamine in Preventing Complications of Iron Overload in Patients with Thalassemia Major N Engl J Med,332, Jan 26, pp 270-273.	N= 59 patients (30 were female and 29 male; age range, 7 to 31 years) were evaluated periodically for 4 to 10 years or until death. At each follow-up visit a detailed clinical and laboratory evaluation and measured hepatic iron stores with a noninvasive magnetic device, were performed.	Each increase of one unit in the natural logarithm of the ratio (transfusional iron load to desferrioxamine use) was associated with an increased risk of impaired glucose tolerance (relative risk, 19.3; 95 percent confidence interval, 4.8 to 77.4), diabetes mellitus (relative risk, 9.2; 95 percent confidence interval, 1.8 to 47.7), cardiac disease (relative risk, 9.9; 95 percent confidence interval, 1.9 to 51.2), and death (relative risk, 12.6; 95 percent confidence interval, 2.4 to 65.4). Conclusions: The early use of desferrioxamine in an amount proportional to the transfusional iron load reduces the body iron burden and helps protect against diabetes mellitus, cardiac disease, and early death in patients with thalassemia major.	Poor
22	Sklar CA, Lew LQ, Yoon DJ, David R (1987)• Adrenal function in thalassemia major following	N= 8 patients with beta-thalassemia who were given	These results indicate that combined multiple transfusions and chelation therapy preserve the	Poor

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	long-term treatment with multiple transfusions and chelation therapy. Evidence for dissociation of cortisol and adrenal androgen secretion. Am J Dis Child, 141(3), Mar, pp 327-30	long-term treatment with combined multiple transfusions and chelation therapy underwent adrenal testing. The six male and two female patients ranged in age from 7 to 19 years.	integrity of the ACTH-cortisol axis in patients with thalassemia.	
22	Grundy RG, Woods KA, Savage MO, Evans JP (***) • Relationship of endocrinopathy to iron chelation status in young patients with thalassaemia major Archives of Disease in Childhood, 71, pp 128-132,	N= 18 patients thought to have been treated by acceptable modern standards, 11 of whom could be considered as well chelated •	The most prominent finding was that growth hormone responses to glucagon stimulation were significantly impaired in all of the patients with iron overload	Poor

ORAL DEFERIOXIMINE /DEFERIPRONE (L1)

No.	Author, title, journal, year, volume, page number	Study design, sample size, follow-up	Outcome and characteristics	Grade & comment
1	Taher A. Chamoun FM. Koussa S. Saad MA. Khoriaty AI. Neeman R. Mourad FH. (1999) Efficacy and side effects of deferiprone (L1) in thalassemia patients not compliant with desferrioxamine. Acta Haematologica, 101(4), pp 173-7	N= 17 patients	Eight patients (47.1%) were positive for hepatitis C virus (HCV) antibodies. Urinary iron excretion was 21.8 14 mg/24 h (mean SD) 1 week after starting DFP and dropped 12 months later to 13 7.4 mg/24 h ($p = 0.009$, paired t test). The initial serum ferritin level was 3,863 2,344 microg/l which dropped to 3,179 2,075 at 12 months after starting therapy ($p = 0.07$). HCV-negative patients as a group exhibited a significant decrease in serum ferritin after 6 and 12 months of DFP therapy (3,942 2,739 vs. 2,341 1,179 and 2,681 1,519 microg/l; $p < 0.03$ and $p < 0.05$, respectively). The most frequent side effects were joint pain, stiffness or swelling in 6 patients (35.3%), and nausea in 7 patients (41.2%), but these were well tolerated and did not require stopping treatment.	Poor
2	Cohen A. Galanello R. Piga A. Vullo C. Tricta	A multi-center trial	Agranulocytosis (ANC < 500/mm3) occurred in	Fair

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	F. (1998) A multi-center safety trial of the oral iron chelator deferiprone. Annals of the New York Academy of Sciences, 850, June 30, pp 223-6.	N= 187 patients F/up: 1 year.	one patient after 15 weeks of treatment, was not accompanied by infection and resolved following treatment with G-CSF. Nine other subjects developed less severe neutropenia (ANC 500-1500/mm3) with the lowest absolute neutrophil count reaching 500-1250/mm3. The neutropenia in these patients developed after 1-50 weeks of therapy, frequently accompanied febrile illnesses, and occurred predominantly in non-splenectomized patients. Reasons other than neutropenia for discontinuing use of deferiprone included nausea (4), voluntary withdrawal (3), high ALT (2), platelet count < 100,000/mm3 (2), low but unconfirmed ANC (1), protocol violation (1) fatigue (1), and depression (1). Mean ALT levels rose within three months of therapy and stabilized thereafter. Arthralgia and nausea and/or vomiting occurred in 6% and 24% of subjects, respectively. In this multi-center trial with weekly monitoring of blood counts, the incidence of agranulocytosis was 0.58 per 100 patient-years, and the frequency of agranulocytosis after one year was 0.5%. These findings support the safety of this formulation of deferiprone, using the careful monitoring system employed in this trial.	
3	Kontoghiorghes GJ, Pattichi K, Hadjigavriel M, Kolnagou A. (2000) Transfusional iron overload and chelation therapy with desferrioxamine and deferiprone (L1). Transfus Sci, 23(3), Dec, pp 211-23)	Review	DF has been a life-saving drug for thousands of patients in the last 40 years. It is mostly administered by subcutaneous infusion (40-60 mg/kg, 8-12 h, 5 days per week), is effective in iron removal and has low toxicity. However, less than 10% of the patients requiring iron chelation therapy worldwide are able to receive DF because of its high cost, low compliance and in some cases toxicity.	Poor

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			In the last 10 years we have witnessed the emergence of oral chelation therapy, which could potentially change the prognosis of all transfusional iron-loaded patients. The only clinically available oral iron chelator is L1, which has so far been taken by over 6000 patients worldwide, in some cases daily for over 10 years, with very promising results. L1 was able to bring patients to a negative iron balance at doses of 50-120 mg/kg/day. It increases urinary iron excretion, decreases serum ferritin levels and reduces liver iron in the majority of chronically transfused iron-loaded patients. Despite earlier concerns of possible increased risk of toxicity, all the toxic side effects of L1 are currently considered reversible, controllable and manageable. These include agranulocytosis (0.6%), musculoskeletal and joint pains (15%), gastrointestinal complaints (6%) and zinc deficiency (1%). The incidence of these toxic side effects could in general be reduced by using lower doses of L1 or combination therapy with DF. Combination therapy could also benefit patients experiencing toxicity with DF and those not responding to either chelator alone. The overall efficacy and toxicity of L1 is comparable to that of DF in both animals and humans. Despite the steady progress in iron chelation therapy with DF and L1, further investigations are required for optimising their use in patients by selecting improved dose protocols, by minimising their toxicity and by identifying new applications in other diseases of iron imbalance.	
4	Richardson DR. (2001)	Review	Despite initial studies showing high Fe chelation efficacy in vitro and also in animals and human	Poor

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	The controversial role of deferiprone in the treatment of thalassemia. J Lab Clin Med, 137(5),May, pp 324-9		subjects, several latter studies have not been so successful. In fact, it has been reported in several clinical trials that deferiprone after long-term treatment had either little effect or actually increased hepatic Fe loading. In addition, an increase in liver fibrosis was noted in one study. However, more recently, results by other investigators have suggested that the drug may be used under some circumstances without marked toxicity. In particular, it has been demonstrated that the combination of desferrioxamine (DFO) and deferiprone results in more Fe excretion than when either chelator is used alone. Moreover, a combination of both drugs led to a decrease in deferiprone-mediated toxicity. Other studies performed in patients for up to 10 years showed no progressive fibrosis after deferiprone therapy, while a possible trend toward increasing fibrosis was noted in another investigation. Additional studies using larger numbers of deferiprone-treated patients are essential to determine the efficacy and safety of this drug, particularly in relation to the development of fibrosis. The present review discusses the possible role of deferiprone in the treatment of Fe overload.	
5	Lucas GN, Perera BJ, Fonseka EA, De Silva DD, Fernandopulle M. (2000) A trial of deferiprone in transfusion-dependent iron overloaded children. Ceylon Med J,45(2), june, pp 71-4	Prospective study. N=54 patients were given a total daily dose of 75 mg/kg of deferiprone orally in divided doses.	Efficacy of deferiprone therapy was assessed by 4-monthly serum ferritin assays using the ELISA technique. Safety of deferiprone therapy was assessed by 4-weekly white cell counts, platelet counts and serum transaminase levels. 54 patients received deferiprone therapy for a mean duration of 9 +/- 3 months. Initial serum ferritin levels ranged from 1500 to 10,700 ng/ml with a mean of 5743. Subsequent serum ferritin levels, obtained in 48	Poor

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			patients ranged from 740 to 7300 ng/ml with a mean of 3558 ($p < 0.001$). In 47 of the 48 patients subsequent serum ferritin levels were lower than initial levels. One child developed severe neutropaenia, which reverted to normal on discontinuation of treatment. 11 children developed arthropathy, which responded to ibuprofen therapy combined in some cases with a reduction of the dose of deferiprone to 50 mg/kg/day. Serum transaminase levels were raised in 5 patients but reverted to pretreatment values or lower despite continuation of deferiprone therapy. CONCLUSIONS: Deferiprone is a safe and effective oral iron-chelating agent which can be used, under strict supervision, in transfusion-dependent iron overloaded children.	
6	Cohen AR, Galanello R, Piga A, Dipalma A, Vullo C, Tricta F. (2000) Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol, 108(2), feb, pp 305-12	Multicentre prospective study. N= 187 patients with thalassaemia major	The incidence of agranulocytosis (neutrophils < 0.5 x 109/l) was 0.6/100 patient-years, and the incidence of milder forms of neutropenia (neutrophils 0.5-1.5 x 109/l) was 5.4/100 patient-years. All cases of neutropenia resolved after interruption of therapy. Neutropenia occurred predominantly in non-splenectomized patients. Nausea and/or vomiting occurred early in therapy, was usually transient and caused discontinuation of deferiprone in three patients. Mild to moderate joint pain and/or swelling did not require permanent cessation of deferiprone and occurred more commonly in patients with higher ferritin levels. Mean alanine transaminase (ALT) levels rose during therapy. Increased ALT levels were generally transient and occurred more commonly in patients with hepatitis C. Persistent changes in immunological studies were infrequent, although	Fair

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			sporadic abnormalities occurred commonly. . Ferritin levels did not change in the overall group but decreased in those patients with baseline levels > 2500 microgram/l. This study characterized the safety profile of deferiprone, and, under the specific conditions of monitoring, demonstrated that agranulocytosis is less common than previously predicted.	
7	Rombos Y, Tzanetea R, Konstantopoulos K, Simitzis S, Zervas C, Kyriaki P, Kavouklis M, Aessopos A, Sakellaropoulos N, Karagiorga M, Kalotychou V, Loukopoulos D. (2000) Chelation therapy in patients with thalassemia using the orally active iron chelator deferiprone (L1). Haematologica,85(2), Feb, pp 115-7	Clinical trial N=11 thalassaemic patients Daily dose of 75-100 mg/kg bw t.i.d	All patients tolerated the L1 well; there were no significant side effects (except for slight gastrointestinal disturbances for the first days). The net urinary iron excretion ranged from 6.96 to 26.1 mg/24h. Serum ferritin declined within 4-6 months in most of the patients. CONCLUSIONS: The results suggest that L1 is a rather safe drug which decreases iron overload without causing any considerable side-effects in Greek thalassemics.	Poor
8	Barman Balfour JA, Foster RH. (1999) Deferiprone: a review of its clinical potential in iron overload in beta-thalassaemia major and other transfusion-dependent diseases Drugs, 58(3), sep, pp 553-78	Review	Non-comparative clinical studies mostly in patients with beta-thalassaemia have demonstrated that deferiprone 75 to 100 mg/kg/day can reduce iron burden in regularly transfused iron-overloaded patients. Serum ferritin levels are generally reduced in patients with very high pretreatment levels and are frequently maintained within an acceptable range in those who are already adequately chelated. Deferiprone is not effective in all patients (some of whom show increases in serum ferritin and/or liver iron content, particularly during long term therapy). . Although few long term comparative data are available, deferiprone at the recommended dosage	Poor

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			of 75 mg/kg/day appears to be less effective than desferrioxamine; however, compliance is superior with deferiprone, which may partly compensate for this. Deferiprone has additive, or possibly synergistic, effects on iron excretion when combined with desferrioxamine. The most important adverse effects in deferiprone-treated patients are arthropathy and neutropenia/agranulocytosis. Other adverse events include gastrointestinal disturbances, ALT elevation, development of antinuclear antibodies and zinc deficiency. With deferiprone, adverse effects occur mostly in heavily iron-loaded patients, whereas with desferrioxamine adverse effects occur predominantly when body iron burden is lower.	
9	Aydinok Y, Nisli G, Kavakli K, Coker C, Kantar M, Cetingul N. (1999) Sequential use of deferiprone and desferrioxamine in primary school children with thalassaemia major in Turkey. Acta Haematol,102(1), pp 17-21	Clinical trial. N= 7 thalassaemic children	None of the patients suffered adverse effects of the therapy but a transient increase in serum ALT levels was noted. A nonsignificant decline in serum ferritin was observed (p = 0.08), a significant reduction in hepatic iron concentration was also determined (p = 0. 03). The hepatic activity index in liver tissues of the patients at the 6th month of the sequential therapy significantly decreased (p = 0.03) whereas fibrosis scores did not differ significantly (p = 0. 25).	Poor
10	Addis A, Loebstein R, Koren G, Einarson TR (1999) Meta-analytic review of the clinical effectiveness of oral deferiprone (L1). Eur J Clin Pharmacol, 55(1), Mar, pp 1-6	Meta-analysis .	Overall, deferiprone has clinical efficacy in achieving negative iron balance and reducing body iron burden in highly iron overloaded patients. After an average of 16 months of deferiprone in doses > or = 75 mg x kg(-1) x day(-1), most patients had a decrease in ferritine concentration.	Good

No.	Author, title, journal, year, volume, page number	Study design, sample size, follow-up	Outcome and characteristics	Grade & comment
11	Wonke B, Wright C, Hoffbrand AV. (1998) Combined therapy with deferiprone and desferrioxamine. Br J Haematol,103(2), Nov, pp361-4	Clinical Trial N=13 transfusion-dependent patients.	These results suggest that increasing the dose of deferiprone or combining subcutaneous desferrioxamine with deferiprone therapy are two methods by which efficacy of iron chelation with deferiprone can be improved in patients inadequately chelated by a daily dose of deferiprone of 75 mg/kg b.w.	Poor
12	Olivieri NF, Brittenham GM, McLaren CE, Templeton DM, Cameron RG, McClelland RA, Burt AD, Fleming KA. (1998) Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. N Engl J Med, 339(7), Aug 13, pp 417-23	Controlled Clinical Trial 72 biopsy specimens from 19 patients treated with deferiprone for more than one year. For comparison, 48 liver-biopsy specimens obtained from 20 patients treated with parenteral desferrioxamine for more than one year	Deferiprone does not adequately control body iron burden in patients with thalassemia and may worsen hepatic fibrosis.	Fair
13	Loebstein R, Dalal I, Nisbet-Brown E, Berkovitch M, Meydan N, Andrews D, Loubser MD, Koren G, Roifman CM, Olivieri NF. (1997) Immune function in patients with beta thalassaemia receiving the orally active iron-chelating agent deferiprone. Br J Haematol, 98(3), Sep, pp 597-600	Randomized Controlled Trial Studied immune function in 57 thalassaemia patients: 36 treated with deferiprone (L1; CP020) and 21 treated with desferrioxamine (DFO).	no clinical or laboratory changes consistent with immuno-suppression or immunodeficiency are observed during deferiprone therapy.	Good

OTHER TREATMENT MODALITIES

HYDROXYUREA THERAPY

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
1.	Hajjar et al (1994)	Case report	Magnitude of rise of Hb varied from 20.3 % to 60 %.	Poor

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
	Pharmacologic treatment of thalassemia intermedia with hydroxyurea Journal of Pediatrics,125(3) , Sep, pp 490-2	N= 3 adult pts	Total Hb increased in all 3 pts followed by a short-term increase with further increase of HU. At high doses , erythropoietic toxic reaction occurred resulting in drop of Hb levels. Total leucocyte count, absolute neutrophil and platelet count remained normal in all patients even when an erythropoietic toxic reaction occurred. No non hematologic toxic effects were observed. Treatment with HU did not result in a sustained increase in total Hb level despite a variable but sustained increase in HbF.	
2	Zeng YT et al (1995) Hydroxyurea therapy in β-Thal intermedia: improvement in haematological parameters due to enhanced β-globin synthesis. British Journal of Hematology, 90(3), Jul, pp 557-63	Case report N= 2 pts F/up 300 days	Transfusion free Total Hb stabilized and then Increased Retic count increased 50 % reduction in both the levels of fetal Hb and F cells after an initial transient increase in percentage of Hb F. Better exercise tolerance and endurance Only side effect: relative neutropenia	Fair Small sample study. Often quoted paper by peers as results shown were promising.
3.	Fucharoen S. (1996) Hydroxyurea increases Hb F levels and improves effectiveness of erythropoiesis in β Thal/ Hb E disease. Blood, 87 (3), Feb 1, pp 887-92	Non randomized prospective trial N= 13 β Thal/Hb E F/ up : 5 mths	Average increase of 33 % in Hb F Decline in HbE from 59 % to 49 % Slight increase in Hb Improved balance in α non α globin chain ratio Minimal side effects	Fair Sample size small Promising results.
4.	Arruda VR et al (1997) Successful Use of hydroxyurea in β Thal major NEJM, 336(13), Mar 27, pp 964	Case report N=1 pt (transfusion dept homozygous β-thalassemia)	Increase in Hb. Transfusions were stopped after 1 year of HU and remained transfusion free at 24 months	Poor 1 case only. Promising.

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
		Follow –up : 24 months		
5	Choudry V.P. et al (1997) Hematological Responses to Hydroxyurea Therapy In Multitransfused Thalassemic Children Indian Journal of Pediatric, 64, pp 395-398	Prospective Trial N=15 children Thal major .	1. Rise in Hb levels seen only in 3 2. Rise in HbF seen only in 3 pts. 3. There was no statistically significant rise in HbF and mean Hb levels.	fair Statistically did not show any significant rise in Hb levels.

BUTYRATES

No.	Author, Title, Journal, Year, Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
1	Perrine et al (1993) A Short term Trial of Buyrate to stimulate Fetal-Globin gene Expression in the β-Globin Disorders NEJM,328(2), Jan 14, pp 81-86	Non randomized prospective trial N=: 6 patients 3 pts with SCD and 3 pts with β-thal syndromes (2 major and 1 intermedia) Short course of IV arginine butyrate for 2 –3 weeks Initial dose 500mg/kg/day and slowly increased to 2000 mg /kg/day in 2 pts Globin-chain ratios, proportions of F reticulocytes were determined before and during treatment	In all patients: Fetal-globin synthesis increased by 6 to 45 percent Proportion of F reticulocytes increased twofold Level of gamma-globin mRNA increased twofold to sixfold. The increase in gamma-globin syntheis led to improvement in the globin-chain ratios One pt had treatment extended to 7 weeks and her Hb increased from 4.7 to 10.2 g% Minimal side –effects. One pt had transient slight rise in serum aminotransferase concentrations concommittantly with a viral infection. Another had transient anorexia.	Fair Promising. Small sample group Setback : needs to be given IV
2.	Sher GD et al (1995) Extended Therapy with IV arginine butyrate in patients with β-hemoglobinopathies.	Non randomized prospective trial. N= 10 pts -5 pts had SCD (4 SC	Primary End points : Thalassemia : No significant changes in total hemoglobin concentration, fetal hemoglobin concentration or imbalance between α- globin and	Fair

No.	Author, Title, Journal, Year, Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
	NEJM, 332(24), Jun `15, pp 1606-10,	anemia 1 Hb S/β), 4 pts had homozygous β 1 pt had Hb E / β IV arginine butyrate for 10 weeks Dose 500 mg/kg/day increased to 2000 mg/kg/day	non α- globin chains observed SCD : Minor increases in fetal Hb Secondary End Points : Changes in ratio of γ-globin mRNA to γ-globin + β-globin mRNA of 1.8 and 3.1 fold were observed. F reticulocytes increased in 2 pts. Extended therapy did not increase total hemoglobin in pts with Thalassemia NOR did it cause sustained increases in fetal Hb in pts with SCD	
3.	Collins et al (1995) Oral Sodum phenylbutyrate therapy in homozygous β thalassemia: a clinical trial. Blood, 85 (1), jan 1, pp 43-9	Non randomized trial N= 12 pts (11 homozygous beta thal of which 3 are transfusion dept and 1 sickle-beta thal) Oral Sodium phenylbutyrate 20 g/day Duration : 41 to 460 days Compliance : 90%	All pts showed increase in %age of F reticulocytes But only 4 pts responded by increasing their Hb levels > 1 g/dl. None of the transfusion dept pts responded Response to treatment was not associated with the type of beta-globin mutation. Baseline erythropoietin levels > 120 mu/ml was seen in all responders (4) and only in 2 of eight nonresponders Side effects : weight gain and /or edema, transient epigastric discomfort in 7 pts and abnormal body odour in 3 pts SPB effective in some pts only And not at all in transfusion dept pts. oral administration	Fair Managed to review only the abstract however, this paper is often quoted by peers.
4	Reich S et al (2000) Oral isobutyramide reduces transfusion requirements in some patients with homozygous β-Thal. Blood, 96(10), Nov 15, pp 3357-63	Non randomized controlled prospective trial. N= 8 pts Transfusion dependent F/ up : 12 mths	1. Hb F increased in all pts from 3.1 % to 6%. 2. 2 responders Compliance : 94 % 1. prolongation of transfusion period 2. decrease of average daily iron by at least 20%	6 Fairly safe drug Oral adm Study small sample size Clinical benefits seen only in 2 out 8

No.	Author, Title, Journal, Year, Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
				pts.

5 AZACITIDINE

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
1	Lowrey et al (1993) Brief report : Treatment with Azacitidine of Patients with End Stage β-Thalassemia. NEJM, 6329 (12), Sept 1, 845-*	Case report N= 3 pts (2 intermedia , 1 major) IV Azacitidine initial dose of 2 mg/kg/day infusion for 4 days at 2-4 week intervals for 30 months.	Increase in peak and trough hemoglobin levels. Transfusion free for all pts. 2 pts better QOL Pt # 3 withdrew from study during 3rd cycle due to personal reasons and died 3 months later. Side effects : dose dependent neutropenia and potential carcinogen. May be beneficial in pts for whom no there is no other treatment options eg life threatening iron overload.	Fair Small sample size. In view of potential side effects, follow up period need to be longer. Setback : IV adm

ERYTHROPOIETIN

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
1	Rachmilewitz et al (1998) The Role of Recombinant Human Erythropoietin in The Treatment of Thalassemia. Annals Ny Acad Sci ,850,June 30, pp 129-138	Expert review of available data	Initial rationale came from animal studies and erythroid cultures. Preliminary studies performed with rHuEPO mainly on pts with Thal Intermedia: No consistent results on the level of endogenous EPO in thalassemias. Experiments on animals showed encouraging results – - gamma-globin synthesis, markedly – increase However, dose required 5 to 10 fold higher than that of Chronic Renal Failure - Role of iron supplementation still unclear HuEPO capable of inducing erythropoietic	Poor Need for well controlled trials. Expensive drug limits the use on a larger scale.

			response in pts withTI who are not regularly transfused - Magnitude of response is dose related Splenectomized pts do better However, the erythropoietic drive resulted mainly in the production of thalassemic RBC since there were no changes in Gamma-chain synthesis, increased levels of HbF and improvement of RBC indices. Expensive drug limits use Combination with other modulators: + HU preliminary results showed positive effects in several erythroid parameters but additive effect on Hb levels not uniformly seen.	

Combination of agents

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
1	Olivieri et al (1997) Treatment of Thal Major with Phenylbutyrate and Hydroxyurea. Lancet, 350 (9076), Aug 16, pp:491-2	Case report N= 2 siblings Treatment : IV arginine butyrate for 7 weeks	Possible to raise the level of HbF production in beta Thal sufficiently to control the disease without transfusion without side effects in certain pts. Suggest that genetic factors may be involved Combination of fetal switching agents shown here to be effective in 2 siblings with thal major. The outcome of these cases displayed evidence Involvement of genetic factors and the nature of Thal mutation	Poor .
2	Dover GJ (1998) Hemoglobin Switching protocols in Thalassemia. Experience with sodium phenylbtyrate and hydroxyurea . Annals NY Acad Sci, 850, Jun 30, pp 80 – 6	Non randomizes controlled prospective trial (ongoing) N= : 14 F/ up : ongoing (3yrs)	36% of all pts or 50 % of non-transfused pts responded to SPB which is considered to be an ncrease in Hb of > 1 g/dl. More studies of this nature necessary to look into the effectiveness of both SPB and HU in the treatment of thalassemia	Fair As study is stilll ongoing , difficult to comment now on the study. .
3	Loukopoulos et al (1998) Hydroxyurea Therapy in Thalassemia Annals NY Acad, 850, June 30, pp 120 – 128	Non randomized controlled prospective trial. N= 62 : 1. 8 pts 2. 10 pts 3. 44 pts	There is a role of HU in beta thalassemic syndromes- it is believed that HU replaced the poorly hemoglobinized, readily sickling and short-lived erythroid cell population with anew cohort of precursors with an active HbF synthesis which end up in a better functioning and longer living red cell population. There is a need for further research and trials before HU or other Hb F inducing agents can be used on a large scale.	Fair

. NUTRITION, TRACE ELEMENTS , VITAMINS , HORMONES AND VACCINES SUPPORT

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
1	De Franceseschi et al (1998) The Effect of dietary magnesium supplementation on the cellular abnormalities of erythrocytes in patients with β thalassemia intermedia. Haematologica, 83(2), Feb, pp 118-125,	N=11 pts with β thal intermedia not requiring chronic transfusion therapy and in 17 normal controls.	In pts with untransfused β thal intermedia , there was reduced erythrocyte Mg and normal serum Mg. In pts given oral Mg supplements, there was significant increases in erythrocyte Mg and significant improvement in characteristic abnormalities of β erthrocytes. The Data indicated that dietary Mg supplementation improves some of the characteristic cellular function abnormalities of β thal intermedia. Apart from, blood transfusions, splenectomy and chelating agents, the role of magnesium replacement may be important in the integrity of the erythrocytes	Fair .
2	Bartfay WJ et al (2001) Selenium and glutathione peroxidase with beta-thalassemia major Nursing Research,50(3), May-June, pp178-83,	Matched case control study N= 20 beta-thal maj and 10 healthy controls	Significantly decreased plasma concentrations of selenium or GPx were observed in pts chelated with L1 or DFO in comparison to healthy controls. Significantly increased concentrations of all measures of body iron burden were observed in beta-thal major. Conclusion : Pts with beta-thal maj and chronic iron overload have decreased concentrations of essential element selenium and the protective selenium-dept antioxidant enzyme GPx. Additional research examining the effects of supplementing dietary selenium is warranted. Replacement of trace elements in diet often forgotten in pts who are on longterm transfusion and on chelation therapy and as such, their replacements impt in maintaining a better QOL in	Poor Reviewed only the abstract. these pts
3	Tesoriere L et al (2001)	N= 15 beta-thal intermedia	Oral treatment with Vit E improves the	Poor

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
	Oral supplements of vitamin E improve measures of oxidative stress in plasma and reduce oxidative damage to LDL and erythrocytes in beta-thalassemia intermedia pts. Free Radical Research,34(5), May, pp 529-40	Monitored for antioxidant status and the lipid oxidation products in plasma,LDL and erythrocytes before and after 9 months oral treatment with 600 mg/day vitamin E.	antioxidant/oxidant balance in plasma ,LDL particles and rbcs and counteracts lipid peroxidation processes in beta-thal intermedia pts Role of Vitamin E ? useful	Managed only to review the abstract.
4	Kajanachumpol S et al (1997) Zinc and copper status of thalassemic children Southeast Asian Journal of Tropical Medicine & Public Health, 28(4), dec, pp 877-80	Investigated the amount of zinc and copper in plasma, erythrocytes and hair in 11 pts with Hb H disease, 59 pts with b thal/HbE disease and 20 pts with homozygous b thal.	Plasma and hair zinc levels were found to be much lower but erythrocyte zinc levels were higher in thalassemic pts than in controls. The levels of copper in both plasma and erythrocytes were higher in pts than in the controls. Mechanism unclear but may reflect the impairment of zinc and copper utilization in tissues in the pathogenesis of these thalassemic pts. Replacement of zinc and copper may be useful	Poor Managed only to get the abstract article. .
5	Fuchs GJ et al (1997) Nutritional Sopport and Growth in Thalassemia Major Archives of Disease in Childhood, 76, pp509-512	N=12 thal pts under 3 yrs of age received intensive nutritional support for one mth and discharged on a prescribed diet of locally available foods. An assessment of anthropometry, bioelectrical impedance analysis and dietary intake was done.	1.Nutritional stunting as the result of reduced nutrient intake is an important cause of growth failure in young children with thalassemia and is responsive to nutritional support. 2.the deficit in height velocity was due to retarded truncal height growth. 3. the bioelectrical impedance analysis method is suitable for body composition analysis. Important for children with thalassemia to receive sufficient nutrition support besides adequate transfusions and chelation therapy.	Fair
6	Kattamis CA et al (1995) Management of thalassemia: Growth and development, hormone substitution, vitamin supplementation and vaccination	Review 1	Hypertransfusion and chelation improves normal growth ,facial and skeletal deformities. Also improves quality of life. Delayed growth and sexual maturation → Growth Hormone Tx does improve growth in	9 Hormonal Replacement may be needed in pts with

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
	Seminars in Hematology, 32(4), oct, pp 269-79		those with severe retardation. → Hormonal replacement recommended for hypogonadism. Diabetes mellitus: Oral HG agents are effective in Mx of glucose disturbances especially in pts with impaired OGTT and delayed insulin secretion. Ketoacidosis – rare Recommendation : i. Normal OGTT but ↑ or delayed insulin secretion → Diet and exercise ii. Impaired or diabetic OGTT → Oral hypoglycaemic agent iii. In nsulin deficiency and diabetic OGTT → insulin if OHG fails Intensive chelation with IV DFO 150 mg/kg/daily 1. Ca2+ and PTH i. hypoparathyroidism → calcitriol replacement 2. Thyroid - Rare 3. Corticosteroids -Important in the role of thal pts with auto- or allo-immunisation to rare red cell antigens. Dosage of 2 mg/kg/day Vitamins Vit C : enhances chelation of iron by DFO, but may also enhance iron toxicity. Supplementation with 200 mg is reserved for established states of depletion and only during treatment with DFO. Vit E : Plasma levels are ↓ Clinical trials failed to show improvement . No indication for use. Folic acid : 2 to 5 mg/ day recommended only for pts with thalassaemia intermedia and irregularly transfused pts with Thal Major. Vaccines Normal immunization sche. For splenectomised pts :	growth and sexual delay and diabetes. Vitamins such as Vit C, E essential , too

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
			→ pneumococcal meningococcal hemophilus influenza	
7	Yesilipek MA et al (1998) L-Carnitine Treatment in Beta Thalassemia Major Acta Haematologica, 100, pp162-163	N=19 patients Homozygous β Thalassemia.	2 pts had significant ↑ in Tx intervals from 4 to 12 –14 wks 1 pt had mild ↑ from 4 to 6 wks Others no change L-carnitine –oral administration Promising. However needs further research. Response in 2 pts leading to freedom of transfusion. Minimal side effects. .	Poor

GENE THERAPY

No.	Author, Title, Journal, Year Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
1	Beuzard Y. (1996) Towards Gene Therapy of Hemoglobinopathies Seminars in Hematology, 33(1), jan, pp 43-52	Review β Thal and sickle cell disease were the first targets for gene therapy.	There is a need for an efficient way to insert genes into hematopoietic stem cells and organization of transferred genetic info that ensures high level expression of the globin gene during erythroid differentiation .	Poor Still experimental.
2	Blau C.A. (1998) Current status of stem cell therapy and prospects for gene therapy for the disorders of globin synthesis. Bailliere's Clinical Haematology 1998 Mar; 11(1): ???	Review Reviews the gene therapy for thalassemia and sickle cell disease.	Describes the efforts 1. improving technology for introducing genes into stem cells 2. developing methods that allow for the selective expansion of genetically modified stem cells.	Poor

OTHER AGENT

No.	Author, Title, Journal, Year, Vol, Page No	Study Design, sample, Size, follow Up	Outcome & Characteristics	Comments
1	Rund D, Fibach E, Goldfarb A, Friedberg A, Rachmilewitz E. (1998) Heme arginate therapy for beta thalassemia: in vitro versus in vivo effects. Acta Haematol,100(2), pp 82-4	N= 4 patients	Hemin has a profound effect on erythroid cell maturation and promotes fetal hemoglobin synthesis in vitro. In beta-thalassemia, increasing fetal hemoglobin levels can ameliorate the anemia. We administered heme arginate, a novel stable form of hemin, to 4 patients with thalassemia intermedia and studied the in vitro versus in vivo effects. In erythroid cultures, there was a marked rise in total hemoglobin and hemoglobin F. In vivo, 3 of 4 patients had a rise in hemoglobin levels (from 0.4 to 1.1 g%), which was statistically significant in 1 patient. There were no serious adverse effects. Heme arginate may be useful in the treatment of thalassemia intermedia.	Poor

PSYCHOLOGICAL THERAPY

No.	Author, Title, Journal, Year, Vol, Page No	Study Design, sample Size, follow Up	Outcome & Characteristics	Comments
1	Anie KA et al (2001) Psychological therapies for thalassemia Cochrane Database Syst Rev (3) : CD 002890	Systemic review of studies done on psychological treatment to improve ability to cope with condition and improvement in both medical and psychosocial outcome.	No trials of psychological therapies were found in the literature at present time.	Good Need for well designed controlled trials to look into the effectiveness of psychological intervention of a chronic illness like thalassemia.

BONE MARROW TRANSPLANTATION

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
1	La Nasa G. Giardini C. Argiolu F. Locatelli F. Arras M. De Stefano P. Ledda A. Pizzati A. Sanna MA. Vacca A. Lucarelli G. Contu L. (2002) Unrelated donor bone marrow transplantation for thalassemia: the effect of extended haplotypes. Blood, 9(12), june 15, 4350-6	Clinical series N=32 24 pts fully matched	69% alive and Tx independent 19% engrafted BUT later died 12% rejected	Poor
2	Yesilipek MA. Hazar V. Kupesiz A. Kizilors A. Uguz A. Yegin O. (2001) Peripheral blood stem cell transplantation in children with beta-thalassemia. Bone Marrow Transplantation, 28(11), Dec,1037-40	Clinical series N=15 PBSCT All phenotypically identical	13 pts well and Tx independent EFS 86.6%	Poor
3	Gaziev D. Galimberti M. Lucarelli G. Polchi P. Giardini C. Angelucci E. Baronciani D. Sodani P. Erer B. Biagi MD. Andreani M. Agostinelli F. Donati M. Nesci S. Talevi N. (2000) Bone marrow transplantation from alternative donors for thalassemia: HLA-phenotypically identical relative and HLA-nonidentical sibling or parent transplants. Bone Marrow Transplantation, 25(8), Apr, pp 815-21	Clinical series N=29 6 relatives 13 mismatched siblings 8 mismatched parents	13 (44.8%) had sustained engraftment Acute GVHD II-IV in 47% Chronic GVHD in 37.5%	Poor BMT from alternative donors should be limited to pts with poor life expectancies
4	Vellodi A. Picton S. Downie CJ. Eltumi M.	Clinical series	EFS 70%	Poor

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
	Stevens R. Evans DI. (1994) Bone marrow transplantation for thalassaemia: experience of two British centres. Bone Marrow Transplantation, 3(5), May, pp 559-62	N=38 Allogeneic BMT	11 deaths Acute GVHD 23.6% Chronic GVHD 28.9%	
5	Lucarelli et al (1998) Bone Marrow Transplantation in Thalassemia ; The Experience of Pesaro Ann N Y Acad Sci, 850, June 30, pp 270-275	Expert review on the state of bone marrow transplant in thalassemia with reference to the study done in Pesaro , Italy. It is still the largest group of performed BMT in thalassemics in the world.	The first BMT in Thalassemia was performed in Seattle in 1981 in an untransfused child with HLA identical sister donor which was highly successful. The first BMT done in Pesaro was on a 14 yr multiply transfused child which was unsuccessful. Analysis of the potential risk factors frm the patients there indicated that the quality of iron chelation, hepatomegaly and portal fibrosis as important risk factors ass with reduced probability of survival and of disease- free survival. These were later classified as Class 1, 2 and Class 3. Class 1 with no risk factors and Class 3 with all risk factors and Class 2 with 1/2 risk factors. Initial results from Class 3 were poor leading to adoption of new preparative regimens which were less toxic. These helped improved the results and pts older than 16 yrs of age are included and they form the grp of adult thalassemics. Probability of survival 78 %, Event free survival 72 % Class 1 Probability of survival 95 %, Event free survival 90 %, Rejection 5 %, Non rejection mortality 5 % Class 2 Probability of survival 85 %, Event free survival 81 %, Rejection 15 %, Non rejection mortality 4% Class 3	Poor The Pesaro group has performed the largest number of BMTs so far in the world today. Their figures show the most impressive survival and disease free survival rates when compared to other centres. Bone Marrow Transplant if done early , with proper pre conditioning regime and with compatible donor does

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
			Probability of survival 78 %, Event free survival 54 % , Rejection 33 %, Non rejection mortality 19 % Continued use of chelating agents helped in the removal of deposited iron in young pts after BMT however, in the older ex-thalassemics, phlebotomy is the treatment of choice . Class 1 pts will achieve relatively normal iron distribution in 1 or 2 yrs after BMT however, those with advanced disease will need some form of removal therapy. For this, EARLY TRANSPLANTATION is favored especially when a suitable donor is available. The range of transplant survival rate among the various International centres offering BMT in thalassemics is from 76 % to 91 % and disease free survival from 53 % to 88 %	offer a good chance of a complete cure in those with thalassemias and dependent on frequent blood transfusions and chelation therapy..

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
7	Lucarelli et al (1993) Marrow Transplantation in patients with thalassemia responsive to iron chelation therapy N Engl J of Med, 329, pp 840-4	Retrospective review N=89 pts Class1 Pesaro Classification Pretransplant condition with busulphan and cyclophosphamide Prophylaxis against GVHD with cyclosporin	Survival - 92 %, Eventfree survival- 85 %, Non rejection mortality - 6 %, Rejection - 8 % 27 % developed Acute GVHD, 4 pts had chronic GVHD 7 pts died all within 101 days of transplant 2 survivors had transient episodes of mixed chimerism without anemia or need for bld transfusion. Clearance of iron overload in the body happens progressively after the 1st yr of transplant. An improvement of survival occurs after the conditioning protocol was changed to Protocol 6 . there is a high probability of complete cure in pts with Class 1 thalassemics who undergo BMT with HLA identical donors.	Poor this study is limited as this not a controlled trial.
8	Giardini et al (1994) Bone Marrow Transplantation for Thalassemia : Experience in Pesaro, Italy Am J Pediatr Hematol Oncol, 16(1), feb, pp 6 – 10	10 yrs study N= 484 pts Allogeneic BMT – HLA identical donor Age 1 to 32 yrs (mean 9 yrs) Liver biopsy done in 398 pts. Stratified acc to risk factors of portal fibrosis ,hepatomegaly and history of chelation adequacy.	Class 1 pts : Probability of survival 97 %, Event free survival 94 % Class 2 pts : Probability of survival 84 %, Event free survival 81 % Class 3 pts : Probability of survival 54 % Event free survival 49 %, 88 of 484 pts died 41 rejected the graft, recurrence of thalassemia (8.5 %) 355 cured of thalassemia (73 %) Commonest cause of death is due to sepsis. Severe acute GVHD 14 %, Severe chronic GVHD 5 % Complications of thalassemia and treatment such as	Fair Same Group of investigators as Lucarelli in Pesaro. Continuous study of those thalassemics transplanted in Pesaro.

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
			diabetes, hepatitis although less severe but still present in 60 – 70 % of children after 15 yrs of age. Class 1 pts tend to achieve relatively normal iron distribution within 1 or 2 yrs but those in Class 2 or 3 may be more difficult. Class 1 and 2 with appropriate marrow donor has a higher probability of being cured by BMT. Recommendation : Patients who have identical HLA identical marrow donors should be transplanted as soon as possible.	
6	GIardini C et al (1995) Bone Marrow Transplanation in Thalassemia Ann Rev. Med , 46, pp 319-30	N=546 transplants. 528 involved genotypically identical siblings 18 – phenotypically identical parents. Classified according to the presence of hepatomegaly, presence of liver fibrosis and quality of chelation.	Class I : 64 pts Mean age : 6 yrs, Mean transfusion : 70, Mean ferritin level : 1576 ng/ml, Pretransplant liver biopsy : Severe iron overload 4 %, Chronic active hepaptitis 4 % Probability of Survival at 10 yrs : 95 % Event free survival 90 % Rejection free mortality 5 % , Rejection 5 %, Acute GVHD 31 % Chonic GVHD 14 % Class II : 188 pts Mean age : 9 yrs, Mean transfusions : 125,Mean ferritin level : 2300 ng/ml,Pretransplant liver biopsy : Severe iron overload 17 %, Chronic active hepatitis 20 %, Mod to severe liver fibrosis 41 % Probablility of survival at 10 yrs : 88 % Event free survival : 85 %, Rejection 4 %, Nonrejection mortality : 12 %, Acute GVHD : 28 %, Chronic GVHD : 16 % Class III : 47 pts Mean age : 11 yrs, Mean transfusions : 70, Mean ferritin level : 3996 ng/ml,Pretransplant liver biopsy : Severe iron overload : 55 %, Chronic	Fair

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
			active hepatitis : 44 %, Mod to severe liver fibrosis: 80 %, Probablility of survival at 10 yrs : 55 %, Event free survival : 53 %, Non rejection mortality 42 % Rejection 9 %, The mortality rates in this Class III group decreased with the introduction of new conditioning regime with a reduced dose of cyclophosphamide however rejection rate also simultaneously increase with this new protocol. Incidence of infections is 51 % with fungal predominance. Usually occurring during marrow aplasia. Acute and Chronic GVHD resulted in deaths in 16 % Lethal Sudden cardiac tamponade occurred in 6 % Limited related HLA matched donors hampers the success of BMT and this results in high GVHD and mortality. Generally, survivors after BMT lead a near normal quality of life for the majority except for those with chronic form of GVHD. The rates of survival in Class 1 and 2 remain the same however, there is some improvement in those in Class 3 after a review of the conditioning regime.	
7	Lucarelli G et al (1999) Bone Marrow Transplantation in adult thalassemic patients Blood, 93, pp 1164-1167	N= 107 adults: Grp A 20 pts Nov 1988 to Jan 1991 Grp B 87 pts Nov 1991 to Sept 96, of which 13 were in Class2 and 74 in Class 3 Ages 17 to 35 Donors HLA identical siblings	Overall survival 66 %, Rejection free survival 62 %,Rejection 4 %,Chronic Active hepatitis was the only risk factor that had a significant impact on survival. For those with no CAH , 75 % survive, For those with CAH, 51 % survive Total of 30 patients died.,50 % died of infections. Most of them were from the group with CAH. Lower doses of preconditioning cyclophosphamide	Fair

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
			although ass with reduced mortality but had an increase in rejection. BMT may be an option to those adults > 17 yrs of age with thalassemia who is on conventional therapy but showing deterioration. However, those who are already showing signs of having Chronic Active Hepatits, there is only a 50:50 chance of survival .	
8	Walters et al (1994) Bone Marrow Transplantion for Thalassemia The USA Experience The American Journal of Pediatric Hematology/Oncology, 16(1), pp 11-17	Desciptive study involving multiple centres N=30 pts 6 different centres in USA F/up::Nov 1981 to April 1992 Modified risk classification used based on liver size, state of iron chelation and serum ferritin level.	Probability of survival was 80 % , Probability of recurrence of thalassemia 24 %, Event free survival was 57 % When classified into good, moderate or poor risk groups, The rate of survival for all groups were the same. Event free survival was slightly better in the good risk grp compared to those in the moderate and the poor risk. 6 pts died after BMT. 3 of them were in the poor risk, 1 in moderate and 2 were good risk. All died within 5 mths of BMT Interesting to note that all those who received total body irradiation as part of the conditioning regimen are alive and free of disease.	Poor Very heterogenous group. Relative small number of patients may have affected outcome. Also different centres with different preconditionin g cytoreductive regimens. No standardization in pretransplant assessment /classification of risk factors. This may have affected the overall similar

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
				results of survival in all 3 groups of risk.
9	Ghavamzadeh A et al (1998) Prognostic factors in bone marrow transplantation for beta thalassemia major : experiences from Iran Bone Marrow Transplanation, 22, pp 1167-1169	N=70 pts F/up: 1991 to 1997	12 died , 1 died 26 mths after BMT due to pneumococcal sepsis. 57 survived Survival rate at 18 mths - 82.6 %, Rejection rate - 11.4 % The longest surviving patient alive and disease free after 6 yrs. Risk factors influencing survival were found to be older age grp (> 9 yrs old), presence of portal fibrosis and increased serum ferritin level. Age was the only poor prognostic risk factor for rejection of the bone marrow transplant. Significant study.Thal Patients in Iran fairly representative of those in developing countries where most patients are poorly transfused and chelated due to multiple factors such as poor socioeconomy, poor accessibility to blood and desferral , poor compliance and sometimes Ignorance on the part of the health care giver.	Fair
10	Chan LL et al (2001) Providing a cure for beta thalassemia major Med Journal of Malaysia, 56(4), Dec, pp 435-40	Retrospective study 43 stem cell transplants 38 pts transfusion dept thal Aug 1987 to June 2000 42 HLA matched sibbblings donors 1 partially matched parent Pre transplant assessment : Class 1 0 Class 2 33 pts Class 3 10 pts	Overall survival : 88 % ,Disease free survival 79 % , Overall transplant mortality 13 % Significant risk factors : age more than 5 yrs and Pesaro Class 3. Patients > 10 yrs old, poor or no chelation therapy , very high serum ferritin levels and having liver fibrosis generally would not do well with transplant One of the few studies done locally on the state of stem cell transplants in Malaysia. The patients involved in this study reflects the state of most of our thalassemics in Malaysia ie most due to socioeconomical reasons are poorly chelated. However, our survival results are comparable to	Fair

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
		Graft : bone marrow 40 pts Cord blood 3 pts	major centres..	
11	Mentzer WC (2000) Bone marrow transplantation for hemoglobinopathies Current Opinion in Hematology, 7(2), Mar, pp 95-100	Review	The results of patients treated with allogeneic matched sibling BMT before the onset of disease –associated organ damage remain at about 90% disease free survival and 5 % transplant associated mortality. Major predictors of death following transplant is the presence of Chronic active hepatitis. The late effects of BMT is almost equal to the adverse effects of iron overload in patients with conventional transfusion and chelation therapy. Overall survival at 25 yrs of age Conventional Tx with chelation therapy - 99 %, BMT - 82 %, Conventional , No chelation - 70 % Experience with use of unrelated donors is still very experimental. There is still active investigations looking into Less toxic conditioning regimens.	Poor Summarises the studies of the Pesaro, North American and the Iranian groups. The state of BMT, preconditionin g regimens , and the state of cord blood transplant. Also, the state of BMT in sickle cell anemia.
12	Piga A et al Late Effects of Bone Marrow Transplantation for Thalassemia Ann NY Acad Sci 1998 Jun 30: 850: 294-9	Retrospective review 33 pts transplanted 1987 to 1995 compared with 155 pts matched for age and treated with conventional therapy. 155 pts were divided into high chelation grp (HC) : 111 pts and low chelation (LC) 44 pts	Median age almost the same for all 3 grps. 14 deaths (BMT 3 HC 1 LC 10), Disease free survival at 25 yrs of life : BMT 82 %, HC 99 %, LC 70 % There was higher incidence of fulminant sepsis and growth impairment in the BMT group Whereas the occurrence of hypothyroidism, hypogonadism and cardiomyopathy higher in those with chelation therapy. There is no statistical differences for the development of diabetes, liver disease and severe infections. The low chelated group show the worst survival and complications like heart failure. However, they show lower rates for sepsis and growth failure probably due to effects	Good to fair One of the few studies comparing the risk and benefits of marrow transplantation to conventional transfusion and chelation therapy. Statistical

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
			of desferrioxamine and conditioning regimens of BMT. The role of phlebotomy in those post BMT seems to be effective in removing iron stores from the body. It appears that conventional therapy with its frequnt blood transfusion and adequates chelation provides almost if not better disease free survival compared to BMT There is also a higher risk of development of sepsis and growth failure too in those transplanted There is still need for longer follow up to monitor BMT related and thalassaemia related complications	adequate.patients for comparison
13	Olivieri et al (1994) Survival in Medicallytreated patients with homozygous beta Thalassemia. N Engl. J Med, 331(9), pp 574-578	Study on 97 pts born before 1976 Mean age 23 yrs old Follow up period 12 yrs Treated with regular transfusions and chelating therapy. Assess the effect of prognostic factors	37 % developed cardiac disease 61 % no cardiac disease; begin chelation treatment earlier, lower mean ferritin level. Estimated Survival without cardiac disease After 5 yrs of chelation - 80 %, 10 yrs -65 %, 15 yrs 55 % Favorable outcome : begin chelation early to maintain a reduced serum ferritin level. Estimated disease free interval 15 yrs after beginning of chelation is 91 % Patients who started chelation later but is able to maintain low ferritin levels do better. In comparison cost between BMT and continuation of blood transfusions and chelation therapy.Estimated cost of BMT(1990) $ 173,250 + Costs of transfusion and chelation $ 32,000 per yr The higher continuing costs of blood transfusion and chelation therapy make them a more expensive option in the long run. The disease free survival for patients who continue conventional therapy is comparable to tose are in class 1 and who opt for bone marrow transplantation. Bone marrow transplantation	Fair Compare the cost different between the 2 forms of treatment

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
			shows that is still more cost effective if does early in class I pts who minimal iron overloads	
14	Woodard P , Lubin B (2002) New Approaches to hematopoietic cell transplantation for hematological diseases in children Pediatr Clin N Am 49, pp 989-1007	Review	<u>Pretransplant Conditioning :</u> Augmentation with fludarabine, azathioprine and hydroxyurea with pretransplant immunosuppressives by the Pesaro Team since 1997 in pts Class 3 and those less than 17 yrs of age was able to produce better survival. <u>Stable mixed chimerism</u>: 10 % of children develop stable mixed chimerism after conventional HLA-identical sibling BMT. This chimerism persisted for 2 to 11 yrs and they remain transfusion independent. Thissuggests that chimerism even with a minority of donor cells might have a curative effect and that full engraftment of donor cells is not required for transplantation. <u>Alternate sources of allogeneic hematopoietic stem cells:</u> Limited experience with alternative donor for thal major.Recent survey of HLA mismatched related donor showed actuarial survival and graft failure rates of 75% and 55% among 64 pts with β-Thalassemia. <u>Newer approaches to alternate donor sources : related and unrelated cord blood::</u> Umbilical cord blood has increased number and proliferative rate of colony forming unit-granulocyte –macrophage (CFU-GM) compared to adult peripheral blood. Also immunologically naïve and lower incidence of GVHD. The ability for cord blood to be stored in	Poor Did not provide latest information on the state of BMT for all types of hematological disorder

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
			public banking programs allows for immediate availability. Less chance of CMV infection. Telomerase activity prolongs the life span of cord blood. More than 2000 cord transplants have been done to date. In the EUROCORD registry, 33 pts with thal received UCBT from a related donor. All survived. 7 experience recurrence . The 2-year event free survival is 79 % which is comparable to bone marrow transplantation These demonstrate the need of a national coed blood banking resource for families with children who might benefit from UCB transplantation. Prevention and treatment of GVHD and haploidentical transplantation: Newer methods to reduce the intensity and toxicity of conditioning as well. as to use highly purified stem cells may allow reduction in GVHD and the use of matched unrelated donors or haploidentical donors	
15	Kelly P. (1997) Umbilical Cord Blood stem cells: Application for the treatment of pts with hemoglobinopathies. J. Pediatr., 130(5), May, pp 695-703	Retrospective review on use of Umbilical Cord Blood (UCB) for transplantion. Rationale exists for collection and storing of UCB stem cells fr pts with hemoglobinopathies , fr siblings and potentially matched donors.	Probability of a thalassemic child with a sibling being HLA identical is only 25 %. In 1980 UCB postulated to be a potential source for hematopoietic stem cell transplantation. No increase in incidence of GVHD with unrelated allogeneic stem cell transplants with UCB, however, rejection rates still remain high .The use of HLA matched sibling donor UCB transplantation recognized and several programs are underway in thalassemic pts. Success of UCB transplantation has pave way for the creation of banks to store UCB for the purpose of research and transplant. There exists both public and privately	Poor

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
			run UCB banks in USA. Ethical issues arise on the ownership, results of testing , privacy and confidentiality and the fair and equitable harvesting and access to stored UCB Less GVHD but engraftment rates same as BMT A UCB banking program could provide a source of matched and mismatched UCB for families with hemoglobinopathies	
16	Chan LL et al (1999) Cure of β-Thalassemia Major by Umbilical cord blood transplantation- a case report of Malaysia's first cord blood transplantation. Journal Trop. Pediat, 45(4), Aug, pp 243-5	Case Study Patient is a 25 mths old β-Thalassemia major. Unborn Sibling found to be a β thal carrier and also HLA compatible. Cord Blood collected at birth.	Transplant done after chemo conditioning. No complications during engraftment. Patient remained well and alive at 9 mths post transplant	Poor
17	Issaragrisil S et al (1994) Brief Report : Transplanation of Cord-Blood Stem Cells into a patient with severe thalassemia Blood Cells,20(2-3), pp 259-62	One case : 2 ½ yrs old girl HbE-β thal reported in Thailand. Transfused 18 units packed cells and on iron chelation. No hepatomegaly Serum ferritin 190 ng/ml Donor from HLA identical infant brother's cord blood	The patient developed catheter related sepsis but responded well to antibiotics. Remained well at 1 yr post stem cell transplant. No features of graft versus host disease.	Poor
18	Reed (2000) Collection of sibling donor cord blood for children with thalassemia. J. Pediac. Hematol. Oncol., 22(6), Nov-Dec, pp 602-4	Bone marrow and Peripheral cord blood transplant provides a potential cure for patients with thalassemia.	In the US, with funding provided by the National Institute of Health, a non commercial Cord Blood Programme was designed specifically to facilitate medically indicated Cord Blood collections from sibling donors. So far, they have collected Cord Blood from 25 thalassemia families in eight states in US. 3 of them have now been used as transplants.	Poor

No.	Author, Title, Journal, Year, Volume	Study design; Sample size; Follow-up	Outcomes and characteristics	Grade & Comments
19	Fang J, Huang S, Chen C, Zhou D, Wu Y Bao R (2002) Allogeneic peripheral blood stem cell transplantation in beta Thalassemia Pediatric Hematology & Oncology 19(7), Oct –Nov pp 453-8	Case Series N= 6	Engraftment was documented in all patients. Acute graft versusu host disease (GvHD) was present in 4 patients but could be controlled with steroid or /and ATG. One patient died of hepatic veno-occlusive disease (HVOD) and survivors were all transfusion independent (ex-thalassaemia). Chronic GvHD occurred in on patient. AllogeneicPBSC transplantation could achieve disease-free survical in beta thalassaemia major patients	Poor

Appendix 1

METHODOLOGY

1 Screening and Prevention

Electronic literature search using PUBMED database was carried out from 1992 - 2002, using the keywords *screening for Thalassaemia* in combination with *prevention program, prenatal diagnosis, cost-effectiveness.* All studies related to the objectives were appraised and graded. A hand search was also done through all international Thalassaemia conference abstracts/proceedings for additional data.

2 Complications

The PUBMED database was used in the search. The search was limited to the complications listed below and literature from 1992-2002 was included. The keywords used were *Thalassemia, Thalassaemia,* in combination with *hepatitis C, hepatitis B, HIV, blood transfusions, complications, short stature, growth impairment, truncal shortening, endocrine complications, iron overload, puberty, delayed puberty, pubertal delay, endocrine complications, iron overload, cardiomyopathy, heart failure, arrythymias, congestive cardiac failure, systolic function, diastolic function, pulmonary hypertension, diabetes, diabetes mellitus, pancreatic reserve, pancreatic functions, insulin, impaired glucose tolerance, bone mineral density, osteopenia, osteoporosis, bone abnormalities, bone complications,*

3 Treatment

3.1 Blood transfusion

An electronic search using PUBMED database was carried out from year 1966-2002, using the following keywords *Thalassemia, Thalassaemia, transfusion regime/ regimen, schedule, filters, alloimmunisation, alloimmunization, cost, Desferrioxamine and social* either singly or in combination. All studies related to the objectives were appraised and graded

3.2 Chelation Therapy

(i) Desferrioxamine

Electronic literature search using Pubmed database was carried out for 1966- 2002, using following keywords *Thalassemia, Thalassaemia,* in combination with *Desferoxamine Desferrioxamine, iron chelation, treatment, toxicity.*

(ii) Deperiprone (L1)

Electronic MEDLINE and OVID search was performed using several keywords and their combinations and limits. There were no relevant titles for many combinations. Search with `thalassaemia OR thalassaemia AND treatment AND side-effects' produced 17 titles of which 12 appeared relevant. Only 7 abstracts were relevant after review of abstracts.
Subsequently, the search was performed without limits using the same keywords. Several articles on the Deferiprone controversy appeared. These involved the industry-sponsored clinical research, the scientific researcher (N Olivieri), the pharmaceutical company (Apotex Ins.), Toronto's Hospital for Sick Children and University of Toronto. Following

that a search on Deferiprone yielded 97 titles of which 76 appeared relevant; 3 reviews of abstracts showed that there were many letters and only 20 abstracts were relevant.

3.3 Haemopoietic Stem Cell Transplantation

An electronic search using PUBMED was carried out from 1992-2003 using the following keywords - *Thalassaemia, thalassemia, bone marrow transplantation, cord blood transplantation, peripheral blood stem cell transplantation, stem cell transplantation,* either singly or in combination. All studies were appraised and graded according to relevance.

3.4 Other treatment modalities

An electronic search of PUBMED database using various keywords as follows: *Thalassaemia; Thalassaemia; management; treatment; hydroxyurea* either singly or in combination from 1992 to 2002 All studies were appraised and graded according to relevance.

Appendix 2

LEVELS OF EVIDENCE SCALE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic reviews.
2	Good	Large sample of RCT
3	Good to fair	Small sample of RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT (CAHTA), SPAIN