Thalassemia Major is common in India. Every year, about 10,000 new patients are diagnosed in India. Treatment requires lifelong monthly transfusions, iron chelation therapy, and other care. A large number of children die before 20 years of age, even before 10 years of age in many rural areas. Average cost of care is Rs. 15,00,000 (fifteen lac) by age 15. Cost goes up with increasing age of child, due to increase in doses of iron chelation, blood transfusion, complications like diabetes, increase in need for investigations and more. Also, about 30% of India’s voluntary blood donation supply is used for thalassemia major transfusion support.

Only known curative treatment is STEM CELL TRANSPLANT/BONE MARROW TRANSPLANT.

How does Transplant help?

It replaces the defective bone marrow of an individual with bone marrow of a person with normal marrow (or thalassemia minor), which then produces normal red blood cells. The patient becomes transfusion free.

Who is a Transplant candidate?

The most critical requirement for transplantation is the availability of a donor. Donor is usually an HLA matched sibling. Other sources like cord blood or matched unrelated donor are increasingly being used.

- Ideal age of transplantation is between 2 to 5 years.
- Patient must be well chelated and serum ferritin should be under tight control (ideally about 1000ng/ml), no hepatomegaly or liver fibrosis.
- Fully matched sibling donor available.
What does Transplantation involve?

1. Donor and Recipient are tested for HLA typing and other genetic tests.
2. Stem cells are collected from peripheral blood or bone marrow using specific protocols.
3. Cells are then preserved in refrigerator. In most cases, cells are infused in patient on same day or next day, hence not requiring cryopreservation (at very low temperatures).
4. Recipient is cleared of “diseased” bone marrow by giving high dose chemotherapy and other medicines, known as conditioning regimen.
5. Stem cells of the donor are then infused in patient, that repopulate the bone marrow and form “healthy” bone marrow and hence normal blood production.
6. Patient needs close monitoring and a number of medicines for at least six months after transplant. Immune suppressive medicines are slowly tapered off, usually over one year period. Some patients need much longer duration.

Approximate stay in the hospital for the donor is 1 day.

Patient is usually discharged in about 4 weeks.

What is the approximate cost of Transplant?

It depends on the size of patient and need for blood products, antibiotics.

Usual cost is about Rs. 10,00,000 (10 lac) plus follow up cost of about 2 lac.

What is the success rate?

About 70-80% patients are cured of thalassemia.
Let us go over the above concepts in more detail.

Thalassemia major is common in India. Disease has serious implications for child, family, society as a whole. Child has uncertain future, with majority of children in India dying before 20 years of age. In families with better resources and motivation, many children now survive beyond 30 years of age. However, this is not easy, and many of them are having serious issues with quality of life due to need for blood transfusion, taking several medicines, and intermittent complications. Also, the financial burden is very high. It is estimated that good quality thalassemia care in India costs about Rs 100,000 per year, for an average child over 10 years of age. Burden on society is also massive. About 30% of voluntary blood donation in our country is utilized for transfusion support of thalassemia major.

The only option for cure for homozygous thalassemia is to transplant healthy stem cells from an HLA-identical donor who is normal or heterozygous (thalassemia minor) for thalassemia, which is capable of producing and maintaining a normal hemoglobin level in the recipient. This procedure is known as Hematopoietic Stem Cell Transplant (HSCT).

**Issues around Thalassemia Transplant:**

Although thalassemia major can be cured by transplant, very few patients undergo this procedure, especially in India. There are several issues related to this decision.

1. Non transplant care of thalassemia major has been steadily improving over the years, with better awareness, better chelation agents, better availability of these agents and safe blood both, more organized thalassemia support groups and transfusion centers. Due to this, quality of life and length of life is improving in India also, however, overall much less than that seen in Italy for example, as noted in graph below:
2. There is also possible hope from “gene therapy” availability in future, which deters patients from going for transplant.

3. Transplant is associated with serious risk of short term morbidity and occasionally mortality. This contrasts with non transplant care, which although not curative, is otherwise comparatively easy. Thalassemia is not life threatening in short term, unlike blood cancers, for which transplant risk is more acceptable.

4. Motivation: very high motivation is required on part of family and child to undergo about 4 weeks of hospitalization followed by several months of strict follow up and treatment, in case of transplant.

5. Cost: transplant although cheaper than long term care of thalassemia, is more expensive in short term. Also, there is a lot of support for non transplant care, such as free blood, free or subsidized chelation, free consultation etc. No or minimal such support exists for transplant.

6. Availability: there are very few centers willing to perform thalassemia transplant, hence patients have to go out of state and travel very long distances which is not feasible for most people as it requires several months of follow up.

7. Donor availability: HLA identical donor is required for transplant, which is possible only in about 25% cases from family. Alternative donor transplants, i.e. out of family donor, is increasingly being used for cancers, but very new for thalassemia.

8. On the other hand, Transplant results are also improving steadily, and number of centers are increasing rapidly. Due to better conditioning regimens, training, better multispecialty hospitals, more trained specialists, and better financial capacity of
society as a whole, there are more patients willing to consider transplant. Also, a slow but steady growth is happening in alternative donor transplants, as there are more patients and transplant specialists willing to take those risks now abroad and in India as well.

9. Best age for transplant is at a younger age. Younger the better. However, most families do not realize seriousness of this disease early, when child is young, and hence do not approach a transplant center. Same is true for many treating doctors, who are not aware of transplant advances, hence do not refer them early enough to a transplant center. Most of pediatricians and family doctors in country were trained at a time when transplant was not available or at least not in their teaching institute. Hence there are a number of misconceptions among doctors as well, about various aspects of transplant. Most parents start thinking seriously about curative treatment only when child develops complications of thalassemia, at which time transplant results reduce considerably.

10. Patient expectations: As thalassemia carries a label of benign disease, and not life threatening in short term, mortality is unacceptable to most parents. Also, thalassemia child otherwise looks near normal, significant post transplant morbidity, especially short term changes in appearance due to medicines like steroids and cyclosporine (facial puffiness, excess facial and body hair, hyperpigmentation of skin) are worrisome for most parents. Chronic gcvd may even create long term changes in appearance. When they see such changes, prospective transplant candidates often delay this curative treatment. Also, media in India frequently hypes negative results more than the positive results. Short term success or failure is highlighted in media a lot more, than long term results. This creates a very difficult situation for parents as they flip flop in their decision making, without having balanced information provided to them.

Who should be offered Transplant:

“All families who have a child with a serious thalassaemia syndrome will be offered the opportunity to discuss bone marrow transplant as a treatment option at an early stage, usually around 12 - 18 months of age. “ – UK Thalassemia Society guidelines 2008.

Decision making regarding whether to undergo a transplant or not, is a very complex one. It depends on many factors, some of them noted in earlier discussion. To help in this decision making, developed countries, as noted above, recommend one visit for all new thalassemia patients to a transplant center. This allows parents to be involved in decision making. In many cases, it leads to a better thalassemia care, as parents see “light at the end of tunnel”. This has been published that patients who are connected to a transplant center generally have better thalassemia care, such as much better iron chelation results.

What is the best age for Transplant:

Ideal age has generally been considered as 2-5 years. Younger the child, less the iron overload, and other complications, hence better the results. This is important to understand, as many parents and doctors in India wait till child is much older, as they feel that older child will “better tolerate” such a big treatment.
However, it is not the age, but the quality of iron chelation which primarily determines outcome. This is well documented in experience of Lucarelli et al, who published the PESARO classification of thalassemia risk status for transplant.

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<th>Chelation</th>
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</tr>
<tr>
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<td>Irregular</td>
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With better pediatric transplant facilities, there are centers in India, who now perform transplant for thalassemia even at age below two years, some even below one year.

Earlier, patients older than 10 years of age were rejected by most centers, due to poor results. However due to better facilities, and safer conditioning regimens, now many patients over age 10 years are transplanted in India. In countries like Italy, where experience of transplant is over 3 decades, patients over 17 years (so called adult thalassemics) are also routinely transplanted, including some even over age 30.

**Who is the ideal Donor:**

Donor is traditionally HLA identical sibling i.e. real brother or sister. However there is only a 25% chance statistically of finding a full match from sibling. Parents rarely are a full match, less than 2% chance, except if there is consanguineous marriage.

A full match or identical donor means at least a 6/6 match. This means six points of HLA locus are same in both patient and donor. HLA typing is done using PCR method. Test is done from a routine EDTA blood sample, requiring only 2 ml blood. There is a low to medium resolution test method and there is a high resolution method.

Low to medium is generally sufficient for test within family. However, high resolution method is mandatory for donor search outside of family. This test can also be done using a swab from buccal mucosa, making it extremely convenient.

Thalassemia minor person can also be a donor. Many parents do not come forward as their normal child is thalassemia minor. This needs to be clarified that thalassemia minor person has a normal life, hence if he becomes a donor, thalassemia major person will be converted to a thalassemia minor. And he will also have a normal life.
For donors from outside family, there are registries worldwide, of voluntary donors. Such registries are now growing fast in India as well. They have the advantage of finding better genetic match, and low cost.

Some centers in world have performed a number of transplants using Umbilical Cord Blood stem cells, with reasonably good success, in tune of 70% thalassemia free survival, and 90% overall survival. Under age of 7 years, their results are even better. However, other centers have not had similar success rates, only about 20% thalassemia free survival, with umbilical cord blood stem cells (New York Blood Center and allied centers). Various reasons have been postulated for this difference.

Lucarelli group in Italy has the largest experience with using mother as donor for stem cells, known as Haplo identical transplant. They have achieved about 60% thalassemia free survival, and 90% overall survival with this method.

Figure: Hematopoietic Stem Cell Transplant from related haploidetical donor. MIH experience on 22 patients of different classes.
How safe is Stem Cell Donation:

This is a frequent question in mind of parents. They do not want to put healthy sibling at risk.

Stem cell donation is an extremely safe procedure. This is evident from the fact that there are over 2 crore (YES over 20,000,000) voluntary stem cell donors worldwide. Even in India, this number is growing fast.

Stem cells can be collected from a child as old as even 9-12 months of age.

Stem cells are collected from bone marrow under general anesthesia, using a procedure similar to bone marrow aspiration. Number of aspirations depend on the number of stem cells required, and weight of the donor. Donor is discharged next day after the procedure, and lives a normal life.

Unlike kidney transplant, there is no permanent loss for donor. Stem cells are plenty in our body, and the lost number is recovered in a matter of few days to weeks. Donor does not feel any different after donation.

What is the process of Transplant:

Transplant is essentially replacing diseased marrow stem cells with healthy stem cells. If we inject stem cells without preparation, patient’s immune system will reject them.

Therefore, patient is first prepared with number of medicines to suppress his immunity. This immune suppression is achieved with high doses of chemotherapy and other medicines or radiation therapy. Such high doses also cause marrow ablation i.e. a picture similar to aplastic anemia, where blood counts are very low. These medicines are given by oral and/or intravenous route. These high doses require hospitalization and special precautions. After delivering these doses, stem cell transplant is done.

“Transplant” in these cases involves infusion of stem cells through a central line. There is no surgery involved. These cells go to bone marrow and start proliferating. It takes about 10-20 days for them to grow and make enough blood cells. During this period, patient needs blood product support, antibiotics, and other special care to ensure safety. Once the blood counts i.e. neutrophils, platelets, red cells recover, patients are discharged. Post transplant, they need many medicines to ensure that donor cells do not react with patient’s body leading to a reaction called GVHD – graft versus host disease. GVHD has many grades. High grade gvhd can be fatal or cause serious morbidity. This care lasts for several months. After several months, immune tolerance develops, and risk of gvhd reduces substantially. Late gvhd can also occur in some cases. Hence close monitoring with transplant center is required for few years at least.

What is the difference between Bone Marrow Transplant and Stem Cell Transplant:

1. Bone marrow transplant is the term used when stem cells are obtained from donor’s Bone Marrow. This was the only source for many years, hence BMT is most famous term.
2. Peripheral blood stem cell transplant is the term used when stem cells are obtained from donor’s peripheral blood. Most cancer related transplants are now done in this manner, for last about 20 years.

3. Umbilical cord blood stem cell transplant means stem cells are obtained from stored umbilical cord blood bank. This is the most recent form of stem cell source.

Unified term for all these transplant sources is HSCT – hematopoietic stem cell transplant or SCT - stem cell transplant. Hematopoietic word is added to differentiate this treatment from other forms of stem cell transplant, such as in the field of cardiology, neurology etc.

All of the above mentioned sources have their advantages and disadvantage. Hence there is no one best source for every patient. Umbilical cord blood, although last one to become available, still is not standard of care especially for thalassemia, and does carry very specific advantages and disadvantages.

Some other terminology:

1. Matched sibling transplant – donor is sibling, with 6/6 match by HLA.
3. MUD – Matched Unrelated Transplant – 6/6 match from out of family, usually from voluntary donor registries.
4. Haplo identical – mismatch transplant from a family member, generally several points mismatch.

**What is the approximate cost of Transplant?**

Cost depends on weight of patient, thalassemia risk class, number of blood products required, number of medicines and monitoring required post transplant, and more. Some of the newer medicines used in conditioning regimen are very expensive, such as treosulfan.

Usual cost is about Rs. 10,00,000 (10 lac) plus follow up cost of about 2 lac.

Unlike government and NGO support for blood transfusion, chelation, blood tests, consultation etc for non transplant care, no such support exists for transplant in India. Thus the only curative treatment for thalassemia is not supported, except rarely by some NGOs or individuals. Structured support for transplant in India is a very recent phenomenon, but still extremely small compared to disease burden.

**What is the success rate?**

Success rate of transplant depends on primarily Pesaro stage as noted earlier. Pesaro class 1, 2 have thalassemia free survival of over 80%, with less than 10% mortality. Pesaro class 3 have significantly reduced results, thalassemia free survival of about 50% and mortality of
about 30%. With newer regimens, in high volume centers, even class 3 have improved results, in range of 70% thalassemia free survival.

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<td>Class 3</td>
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**SUMMARY**

- SCT remains only curative option.
- All patients are not candidate for SCT.
- A number of eligible and motivated patients exist who should undergo SCT.
- SCT centers with thalassemia focus will improve numbers and results.
- Alternative stem cell sources need to be considered.
- SCT center presence has positive effects on thalassemia care in the region as a whole.

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