DEPARTMENT OF CLINICAL HEMATOLOGY

What is blood?

Blood is the vital fluid of the body, which performs diverse functions from delivering oxygen to each and every cell of the body to fighting against infections and control bleeding.

Blood contains three types of blood cells each with a distinct function.

- **Red blood cells –** which carry oxygen around the body
- **White blood cells –** which help fight infection
- **Platelets –** which help stop bleeding

In keeping with different types of blood cells and their function, diseases of blood include a variety of diseases. They can be divided in benign blood diseases or malignant diseases (cancers).

Benign blood diseases include anemias like thalassemias, sickle cell anemia, hemoglobinopathy, aplastic anemis etc. diseases of blood may cause clotting problems like deep vein thrombosis/antiphospholipid antibody syndromes. Bleeding disorders like hemophilia and rarer coagulation factor deficiencies. Dysfunctions of white blood cells give rise to diseases of immunodeficiency.
Malignant diseases or blood cancers include acute leukemia (acute myeloid leukemia, acute lymphoblastic leukemia), chronic leukemia (chronic lymphocytic leukemia, chronic myeloid leukemia), non-hodgkins lymphoma, hodgkins disease, multiple myeloma and myelodysplastic syndrome.

Bone marrow

A fraction of blood cells die every day which is replaced by new cells formed in bone marrow. Bone marrow is the tissue, found in the flat bones of our body. Bone marrow contains hematopoietic stem cells (HSCs), the primitive cells which give rise to mature blood cells.

Bone marrow transplant (BMT) or hematopoietic stem cell transplant (HSCT) is a procedure in which a patient's diseased bone marrow is replaced with healthy bone marrow/stem cells.

Indication of BMT/HSCT

Bone marrow transplants are often needed when a person's own bone marrow has been damaged and can no longer produce normal blood cells. Bone marrow transplants are usually only recommended if:

- the recipient is in relatively good health despite their associated condition (which is why they're often carried out when cancer is in remission)
- stem cells are available from a brother/sister or, less commonly, another family member, or an unrelated donor with the same or similar tissue type (this reduces the chances of the bone marrow being rejected)
- the associated condition isn't responding to other forms of treatment and it's believed that it would respond to a transplant and could get worse without one
- the benefits of a transplant are believed to outweigh the risks.

Risks

- Bone marrow transplants are complicated procedures with significant risks.
- GVHD: In some cases, the transplanted cells (graft cells) recognize the recipient's cells as "foreign" and try to attack them. This is known as graft versus host disease (GvHD). The risk of infection is also increased because your immune system is weakened when you're conditioned (prepared) for the transplant.
- Chemotherapy/radiotherapy: The major problem with stem cell transplants is the recipient's ability to withstand high doses of chemotherapy (and sometimes radiotherapy), which are often needed before the transplant.

- **Infection:** After having a bone marrow transplant, risk of developing an infection will increase. This is because the conditioning given before the transplant weakens our immune system. The risk of infection may be increased further if patient need to take immunosuppressants. It's very important to prevent infections developing. If one gets an infection it could quickly develop into a more serious condition, such as a lung infection (pneumonia).

Some of the diseases of blood/marrow that require transplant are as follows:

1. Bone marrow failure

The all human beings blood cells are continuously made to replace old/dead cells. This production of new blood cells only occurs in bone marrow. Therefore, a bone marrow transplant may be needed if your bone marrow fails (known as severe aplastic anaemia).This may happen as a consequence of an inherited conditions like fanconi anemia, dyskeratosis congenital, diamond blackfan anemia (pure red cell aplasia), amegakaryocytic thrombocytopenia etc.BMT/HSCT is the only curative treatment for these disordrers. More commonly aplastic anemia is not inherited and presents as an acquired condition. Precipitating cause of acquired aplastic anemia is not known but there is an immune mediated destruction of stem cells resulting in aplastic anemia. BMT/HSCT is indicated for the treatment of young patients (less than 40-45 years of age with matched family donor) or patients who fail immunosuppressive therapy.

2. Acute Leukaemia (AML/ALL)

Leukaemia is cancer of the white blood cells. The acute leukemias white blood cells replicate in an uncontrollable manner and don't develop into normal infection-fighting cells. The cancerous cells can quickly spread through bloodstream, leading to a lack of room for the production of normal red blood cells and platelets. Acute leukemia present with symptoms of anaemia, infection and bleeding.

There are numerous types of leukemia where a bone marrow transplant may be needed. These are:

- Acute lymphoblastic leukaemia (ALL)
- Acute myeloid leukaemia (AML)

3. Chronic leukemia:

Chronic leukemia is also abnormal proliferation of white blood cells. Usually these diseases progresses slowly and transplants are required once they are not controlled by medicines. Chronic leukemia includes:

Chronic lymphocytic leukaemia (CLL)
Chronic myeloid leukaemia (CML)

4. Non-Hodgkin lymphoma

Non-Hodgkin lymphoma is cancer of the white blood cells but unlike leukaemia, it spreads through the lymphatic system.The lymphatic system is a series of connected glands (lymph nodes) that are located through out our body. It's an important part of the immune system, which makes our body's natural defence against infection and illness.

5. Genetic blood and immune system disorders

There are number of blood disorders where mutations (alterations) in genes cause the blood cells to develop abnormally. These include sickle cell anaemia and thalassaemia. Both conditions interfere with the production of red blood cells. Immune system disorders can include a wide range of immunodeficiencies and some other genetic conditions.

6. Multiple myeloma/amyloidosis

Multiple myeloma is a disease in which a special type of cell known as plasma cell turns cancerous. Normally plasma cell makes antibodies which functions to fight infections. In myeloma plasma cells proliferates and instead of making normal antibodies, makes defective proteins called paraprotein. Myeloma presents with symptoms of bone pains, spontaneous fractures, kidney failure, anemia and repeated infections. In amyloidosis plasma cells makes paraproteins which is deposited in different organs of body like heart, kidney, nerves, liver and intestine and results in their malfunction. Autologous stem cell transplants is part of standard treatment of young/fit patients of myeloma and amyloidosis.

Procedure of bone marrow transplant

A bone marrow transplant involves taking healthy stem cells from the bone marrow of one person and transferring them to the bone marrow of another person. This is known as allogenic transplantation. In some cases, it may be possible to take the bone marrow from patients own body. This is known as an autologous transplantation. High dose chemotherapy is given to kill the cancer cells before stem cells are returned to the patient.
A bone marrow transplant has five stages. These are:

- **Planning**
- **Pretransplant work up**
- **Harvesting**
- **Conditioning**
- **Bone marrow/ stem cell infusion**
- **Engraftment**
- **Follow up**

Planning

Before starting the preparation for transplant following issues need to be discussed including Timing of transplant, hospital stay, Fertility, Early menopause, Clean diet, Losing hair and risk of prolonged morbidity and potential mortality.

Pre-transplant work up

Having a bone marrow transplant can be an intensive and challenging experience. Many people take up to a year to fully recover from the procedure. A thorough physical examination is done before a stem cell transplant. As part of the examination, some scans to check the condition of internal organs, such as your liver, heart and lungs is performed. A bone marrow biopsy is performed before transplant in cases of hematologic malignancies (leukemia/lymphoma/myeloma). The results of the biopsy will show whether your cancer is in remission (under control) and whether there's a high risk of it returning after your transplant. Allogenic transplants are performed once a suitably HLA matched family/unrelated donor is available. Before taking the donor for stem cell donation a thorough general physical examination is done. Some blood tests are also done on donor to assess liver/kidney function and status of viral infections.

Stem cell mobilization and harvesting

Stem cells are harvested only after donor is found fit for donation (or in cases of autologous transplants disease is in remission). The method most commonly used in adults involves removing stem cells from blood by using apheresis machine. This machine separates stem cells from the other cells in the blood and then blood is returned to the body. For stem cells

to be collected in adequate numbers, growth factor (G-CSF) is given for 4-5 days. Growth factor mobilizes stem cells from bone marrow to blood which are then collected. G-CSF can cause mild side effects like fever, body pain etc but carries no long term hazard.

An alternative method is to collect the bone marrow itself by removing stem cells from the hip bone using a special needle and syringe. This may be recommended for certain conditions that require a transplant, or if the donor is a child. Bone marrow collection is done under general anesthesia. Depending upon the cell's source transplant can be autologous or allogenic.

Autologous transplantation

It may be possible to use patient's own stem cells, providing they're suitable. This is known as an autologous transplantation. They can be harvested using either method described above.

If bone marrow is being extracted, a needle will be used to remove around a litre of bone marrow. It will usually be removed from your hip bone, under general anaesthetic.
The procedure is low risk, but the area where the needle is inserted may be painful afterwards. The harvesting process may sometimes need to be carried out a number of times before enough bone marrow is obtained. After being extracted, your stem cells may need to be treated with radiation or chemotherapy to ensure there are no cancerous cells left.

Allogeneic transplantation

If patient's own stem cells aren't suitable, stem cells will be harvested from a healthy donor. This is known as allogeneic transplantation. For allogenic transplants tissue typed (HLA matched) donor is required. All human tissue carries a special genetic marker or code, known as a human leukocyte antigen (HLA). For a transplant to be successful, the transplanted tissue should ideally come from someone with an identical or very similar HLA tissue type. If the transplanted tissue has a different HLA type, your immune system might treat it as a foreign object and reject it.Alternatively, the cells from the transplanted tissue may regard the rest of your body as a foreign object and start attacking it. This is known as graft versus host disease (GvHD).Our tissue type is inherited from both parents. If a patient has a brother or sister who's willing to be a donor, they'll need to be tested to see whether their HLA type is the same as patient's.There's a one in four chance of each full sibling (those who share the same parents) being an exact match.If siblings aren't suitable donors, a search for unrelated donors in international HLA registries can be carried out. It holds the details of people who are willing to donate stem cells and their HLA type. It may take several months before a suitable donor can be found. Sometimes waiting without treatment may be considered too dangerous, or finding a full match may not be possible. In

such cases, stem cells from a partially matched donor (haploidentical) may be used. This will increase the chance of complications, but your treatment team may recommend it if the potential benefits outweigh the risks.

Donor and patient can be fully HLA match or differ in one or more HLA antigens. In around 30% of cases, a family member, such as a brother or sister, is a fully matched donor. HLA half match donors (haploidentical) are available to virtually all patients among parents, children and siblings. In 70% of patients a suitable donor can be found through international donor registries or in form of half matched donors. Finding a suitable stem cell match is often difficult due to a lack of volunteers. In particular, there's a shortage of donors from African, African-Caribbean, Asian, Jewish, eastern European and Mediterranean communities.

The more people who register, the more chance there is of finding a matching tissue type for someone who needs a transplant. When a suitable donor is found, their identity and location, and those of the patient, remain confidential.

The methods of harvesting cells from a healthy donor are similar to those used for an autologous transplant (see above). For four days prior to the transplant, the donor is given medication (G-CSF) to stimulate the production of stem cells in their blood. On the fifth day, they'll have a blood test to check they have enough circulating stem cells. They'll then be connected to a cell-separator machine. A general anesthetic isn't needed, which means the harvesting can be carried out as an outpatient procedure. Blood is removed through a vein in one arm and passed through a filtering machine, to separate the stem cells from other blood cells. It's then returned to the body through a vein in the other arm. If the number of cells obtained is insufficient, the donor may be asked to return on the sixth day to make another donation. The procedure usually requires about two sessions lasting four to six hours on successive days.

Removal of bone marrow from the hip bone is carried out in hospital, under general anesthetic, using a needle and syringe. Although it's not a surgical operation, some marks from the needle will be left on the skin. There may also be some discomfort where the needle is inserted.

The donor will need to stay in hospital for up to 48 hours and have an at-home period of recovery lasting up to five days.

Conditioning

As part of your conditioning, patient need to be given a range of medicines, meaning a tube will be inserted into a large vein near your heart. This is known as a central line and is used instead of many (often painful) injections.

The conditioning process involves using high doses of chemotherapy and sometimes radiation. It's carried out for three reasons:

- to destroy the existing bone marrow cells to make room for the transplanted tissue
- to destroy any existing cancer cells
- to stop your immune system working, which reduces the risk of the transplant being rejected

The conditioning process usually takes between four and seven days. You'll probably need to stay in hospital throughout the procedure. Side effects from chemotherapy are common and include:

- nausea (feeling sick)
- vomiting
- diarrhoea
- loss of appetite
- mouth ulcers
- tiredness
- skin rashes
- hair loss

Side effects can last for several weeks after conditioning has finished, although mouth ulcers and skin rashes should stop once the transplanted tissue begins to produce new blood cells. Hair usually grows back within three to six months.

Two less common, but potentially very serious, side effects of the conditioning process are lung damage and a condition called veno-occlusive disease.

Lung damage or a lung infection can be treated with oxygen, antibiotics and other treatments. Steroids (strong medication) may also be given to dampen potentially dangerous immune reactions.

Veno-occlusive disease causes the blood vessels in your liver to swell, stopping it from removing waste products from your body. This can cause abdominal pain, jaundice (yellowing of the skin and whites of the eyes) and weight gain.

Veno-occlusive disease can be treated with medicines to help prevent blood clots, as well as using blood transfusions and reducing the amount of salt in your diet.

The transplant

It's usually possible to carry out the transplant one or two days after conditioning has finished.

The donated stem cells will be passed into your body through the central line. This process can take anywhere from half an hour to several hours to complete, depending on the type of blood cells being used.The transplant won't be painful and the patient is awake throughout the procedure.

Engraftment

Patient may feel weak after the transplant, and may experience vomiting, diarrhea and/or a loss of appetite. To prevent malnutrition (a lack of essential nutrients), patient will need to have nutritional support, with high-protein fluids taken by mouth or through a tube running from your nose to your stomach.

The first stage of the recovery process involves waiting for the stem cells to reach your bone marrow and start producing new blood cells. This is known as engraftment and usually occurs 15-30 days after the transplant takes place. During this period, you'll need to have regular blood transfusions, as you'll have a low number of red blood cells.

The risk of developing an infection is also increased, because patients have a low number of white blood cells. This means that you'll need to stay in hospital, in a germ-free environment.

Patients may be allowed visitors, but they may have to wear surgical gowns and hats to prevent infection. Antibiotics may also be used to either prevent or treat infections. Many people are well enough to be discharged from hospital between one and three months after undergoing a bone marrow transplant. However, if someone develop complications, such as an infection or GvHD, one may not be able to leave hospital for more than three months after the transplant

Follow up

Once engraftment has occurred, patient’s bone marrow will begin to produce blood cells. Patient’s still have a high risk of developing an infection, as it can take as long as one to two years for your immune system to return to full strength. Patients need to be given medicines that stop immune system from working (immunosuppressants), to prevent graft versus host disease (GvHD). In some cases, the transplanted cells (graft cells) recognize

the recipient's cells as "foreign" and try to attack them. This is known as graft versus host disease (GvHD) and often occurs after stem cell transplantation.

There are two types of GvHD:

- **Acute GvHD** – which usually occurs during the first three months following the transplant
- **Chronic GvHD** – which may develop from acute GvHD and can cause symptoms for many years

The symptoms of **acute GvHD** include:

- red spots on the hands, feet and face
- fever
- bloody or watery diarrhea
- stomach cramps/pain
- jaundice

Chronic GvHD can develop at any time between three months and two years after the transplant. The symptoms can persist or may come and go for many years. They can range in severity from mild to life-threatening.
Symptoms of chronic GvHD include:

- an itchy, dry rash that can spread over the entire body
- hardening of the skin
- dry and sensitive mouth
- dry eyes
- hair loss

In particularly serious cases of GvHD, lung or liver function can be affected, which can be very serious.

GvHD is treated with immunosuppressants, usually in combination with corticosteroids.
Immunosuppressants stop the transplanted stem cells attacking the rest of your body. However, they'll also affect the rest of immune system, placing the patient at a higher risk of infection.

Corticosteroids are powerful medications that can help suppress (control) the exaggerated immune response that leads to GvHD. However, corticosteroids can cause a number of side effects, including:

- high blood sugar levels
- increased appetite
- mood changes

- diarrhea and vomiting
- itchiness
- high blood pressure (hypertension)