INTRODUCTION

Bone marrow transplantation (BMT) is the treatment of choice for many immunological deficiency diseases of childhood and offers a reasonable chance of cure for several childhood cancers. The BMT is an intravenous infusion of bone marrow cells from the donor to pediatric patient (the recipient). The prime purpose is to replace or stimulate a non functioning bone marrow. There are three types of BMT, allogeneic (similar donor), autologous (the child's own bone marrow is removed, sometimes treated to kill diseased cells then reinfused) and syngeneic (from an identical twins) ***(Meadows et al., 2001).***

However the incidence of BMT in Egypt is underestimated but the first trial for BMT was carried out in the National Cancer Institute (NCI), Cairo university in April 1988. Allogeneic BMT in 576 pediatric patients and total autologous BMT in 105 pediatric patients were done from 1997 to 2008 at Nasser Institute. And total autologous BMT in 71 pediatric patients were done from June 2008 to 2010 at Sheikh Zayed Specialized hospital ***(Mahmoud, 2010).***

The clinical pathways have been developed in health care as multidisciplinary care plans that outline the sequence and timing of actions necessary for achieving the expected patient outcomes and organizational goals regarding quality, cost, pediatric patient satisfaction and efficacy ***(El Baze et al., 2007).***

The clinical pathway represents a standardize, integrated multidisciplinary care plan, which includes the assessment and care given by all disciplines involved with patient's care. Its purpose is to help coordinate health care services and decrease costs associated with duplication of effort. Using a clinical pathway helps to optimize quality, efficacy and organization of health care delivery services. A clinical pathway requires the active understanding of care principles and participation of health care team including pediatric patient ***(Arnold and Boggs, 2007).***

The elements/components of clinical pathway include patient population, time frames, interventional categories, outcomes and variance record ***(Nancy and Holloway, 2004).***

Nurses have played an important role in the success of BMT with their involvement in day to day care as well as research. The pediatric nurses are continually being challenged to meet the physical and emotional needs of the child and family. The nurses role during preparation to BMT unit is of critical importance. However nurses provide both direct and indirect care throughout all phases of a child's transplant course. Working closely with physicians, social workers, dietitions, pharmacists, physical therapist and others, the nurse serves as a link between the family unit and the medical team ***(Ballen, 2005, Timby and Smith, 2003).***

Nurses have a key role in all aspects of clinical pathways. It includes identify how bone marrow transplant team work, providing direct care, complete the required documentation, discuss the pathway with the patient and focuses on achieving patient's outcomes, participating in the development, implementation and continuous evaluation of any pathway. Nurses need to understand their roles in helping ensure that best practices and good patient care are incorporated into clinical pathways. The pediatric patient/family teaching is a crucial aspect of clinical pathway. Ideally, the pediatric patient/family receive a simplified version of the pathway which the nurse review with the pediatric patient and family daily. The standardized teaching protocols, described in the pathway, give the nurse detailed guide in teaching for both current and discharge what patient's needs ***(Smeltzer and Bare, 2009)***

AIM OF THE STUDY:

a) Assess the nurses' knowledge regarding effect of nursing clinical pathway on care of children undergoing bone marrow transplantation.
b) Implement the nursing clinical pathway in care of children undergoing bone marrow transplantation.
c) Evaluate the effect of nursing clinical pathway on the patient's outcomes.

RESEARCH HYPOTHESIS:

There is a positive effect of nursing clinical pathway on care provided by nurses to children undergoing bone marrow transplantation.

REVIEW OF LITERATURE

History of Bone Marrow Transplantation

The word transplant refers to a complete organ or a section of tissue that is removed from its original site and transferred to a new position in the same person or in a separate individual. Transplantation and grafting means the same thing, while the term grafting is more commonly used to refer to transfer of the skin. Early attempts to transplant marrow in human were largely unsuccessful. Bone marrow was first used to treat humans disease in (1891) by Brown-sequared. The procedure was described as an extract of marrow and was given by mouth for patients with pernicious anemia and leukemia ***(Zaghloul, 2004, Dreger and Schmitz, 2001).***

Bone marrow was administered intramuscularly in (1937), by Schretzenmayr. These early attempts were soon followed by unsuccessful attempts to use marrow given by the intramedullary and intravenous routes, by the late (1960s) the medical research focused on the importance of human tissue typing and applied this concept to organ and marrow transplantation. Successful allogeneic transplants were performed in increasing numbers, simultaneously, the technology of platelet transfusion and methods of prophylaxis against infection were developed ***(Pamphilon et al., 2009).***

The first successful allogeneic bone marrow transplants in human were carried out in (1968). Since then, use of allogeneic or autologous hematopoietic stem cell transplantation has increased dramatically, with an estimated 40-50.000, hematopietic stem cell transplantations (HSCTs) worldwide in (2011). The team of the National Cancer Institute (NCI), Cairo university, has pioneered this field in Egypt and started an allogeneic and autologous BMT program since (1988) with over 1000 transplants performed over the past 8 years. The team of the National Cancer Institute was the first team in Egypt who started the use of peripheral blood stem cell (PBSC) as a source of stem cells both in allogeneic and autologus settings ***(Mahmoud et al., 2011).***

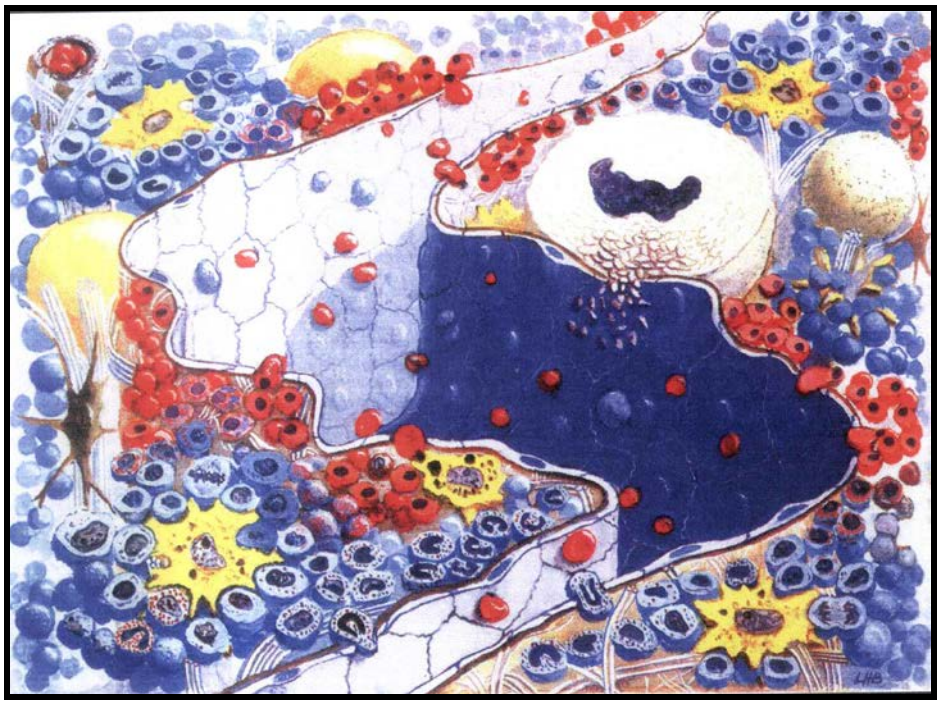
The first successful unrelated umbilical cord blood transplant was performed by J. Kurtzberg and pediatric transplant team at Duke university in (1993). In (1988), umbilical cord blood (UCB) hematopoietic stem cell (HSC) from a related sibling were transplanted successfully into a child with fanconi anemia ***(Gluckman, 2009 and Ballen, 2005).***

Anatomy and Physiology of Bone Marrow

The bone marrow is a vital organ in the body, it is a soft spongy tissue which is found inside the bones. The bone marrow which is found in spine, ribs and skull contains cells that produce the body's blood cells.The bone marrow after development store about 95% of the blood cells. This bone marrow produces red blood cells, white blood cells and platelets. Each of these cells contain a life maintaining function. Normal functioning bone marrow is rich with progenitor or stem cells which eventually proliferative into mature erythrocytes, leukocytes and platelets ***(Zaghloul, 2004).***

Bone marrow, also called myeloid tissue, which is the main site for blood cell formation and it consists of blood vessels, nerves, mononuclear cells, phagocytes, stem cells, blood cells in various stages of differentiation and fatty tissue. There are two types of marrow, the first one is yellow or inactive marrow: consists of a basis of connective tissue, supporting numerous blood vessels and cells, most of which are fat cells, although a small population of typical red marrow cells persists. Yellow marrow has no significant haematopoiesis ***(Farhi et al., 2004).*** The second one is red or active (haematopoietic marrow), the red marrow consists of a network of loosely woven connective tissue, the stroma, supporting the cluster of haemopoietic cell (haemopoietic cords or islands) (figure,1) and a rich vascular supply in which large, thin walled sinusoids are prominent. The stroma also contains a variable amount of fat, depending on age, site and the haematological condition of the body, small patches of lymphoid tissue are additionally apparent. The marrow consists of two major compartments, are vascular and the other extravascular. The whole assembly is enclosed within a bony framework, from which it is separated by a thin layer of bone lining cells ***(Hoffman et al., 2009 and Hoffbrand et al., 2002).***

Figure (1): Microscopic organization of bone marrow depicting a sinusoid in section, showing haemopoietic islands centered on macrophages (yellow), forming erythrocytes (red), various classes of leucocytes (blue), megakaryocytes (beige), adipocytes (orange), fibroblasts (brown) and endothelial cells (dark blue-purple) flanked by a basal lamina and reticulin fibers (white). A group of platelets (white) and various other cellular types are shown passing through apertures in the endothelial linings of sinusoids.



Williams, P.L., Dyson, M., Warwick, R. and Bannister, L.H., (1989): Gray's anatomy, 37th ed., Churchill Livingstone, London 675-682.

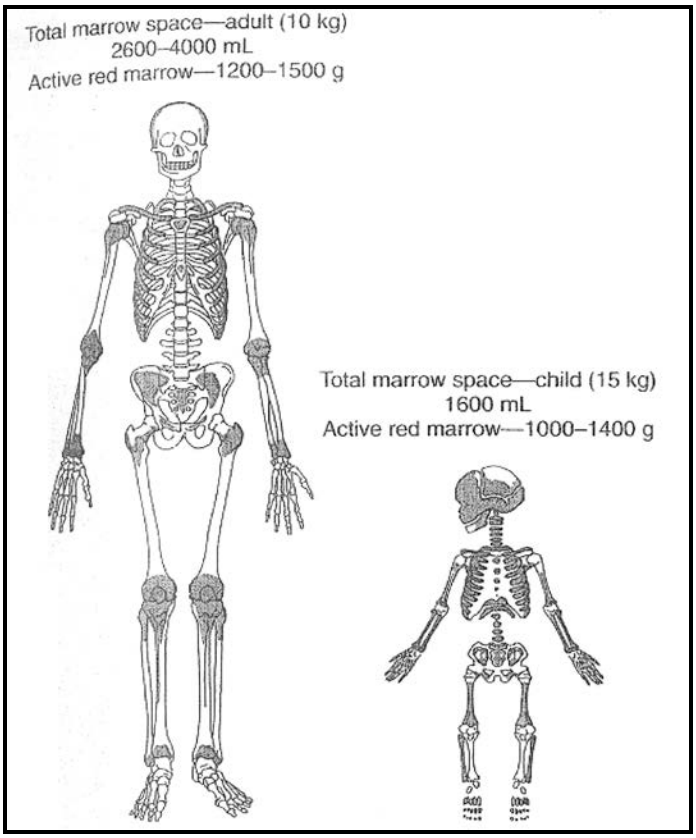
The stroma is composed of a delicate network of fine collagen (reticulum) fibers secreted by and adherent to a highly branched adventitial reticular cells which appear to be a type of fibroblast and derived from embryonic mesenchyma. When haemopoiesis ceases, as in some limb bones in an adult life, filling the marrow with yellow fatty tissue, but if there is a later demand for haemopoiesis, this cells change back to their earlier stellate form ***(Snell, 2002).***

Endothelial cells line the marrow sinusoids, the single layer of cells being supported by reticulum fibers on its basal surface. Endothelial cells are connected by tight junctions, which appear to be effective barriers between vascular and extravascular spaces.The passage of newly formed haemol cells from the haematopoietic compartment into the blood stream occurs through temporary a pertuses formed in the endothelial cell

cytoplasm, the migrating cell filling tightly as it passes through the aperture closing immediately behind it ***(Orkin et al., 2009, Bishop and Pavletic, 2008*).**

At birth the marrow of all the bones of the body is red and haematopoietics. This blood forming activity gradually lessens with age and the red marrow is replaced by yellow marrow. The relative red (active) marrow space of child is much greater than of an adult because the high requirements for red cell production during neonatal life demands, the resources of the entire production potential of the marrow (figure, 2) ***(Orkin et al., 2009).***

Figure (2): Comparison of active red marrow-bearing areas in a child and adult. (Note the almost identical amount of active red marrow in the child and adult despite a fiver fold discrepancy in body weight).



Orkin, S., Nathan, D., Ginsburg, D., Look, A., Fisher, D., and Luxiv, S. (2009): Nathan and oskis hematology of infancy and childhood, 7th ed., Saunders El Sevier, Philadelphia 195-207.

Haemopoietic tissue, cords and islands of haematogenous cells consists of clusters of immature haemol cells in various stages of development, typically several different cell lines being presented at each focal group, one or more macrophages of a dendritic

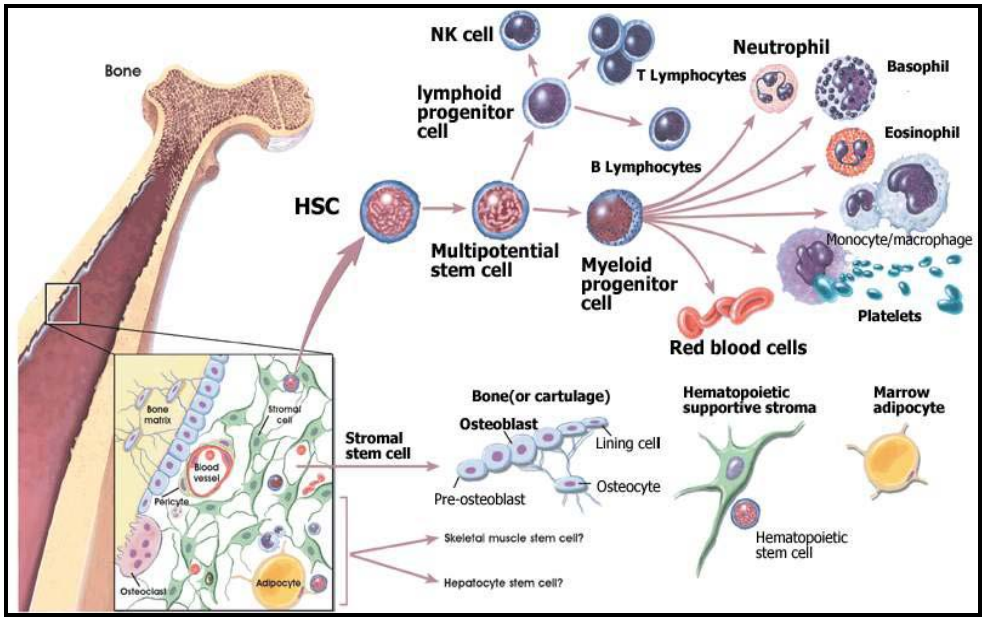
shape, line at the cores of each such groups of cells and may contain the iron bearing molecules ferritin and haemosiderin, besides the phagocytic that such macrophages are important in transferring iron to develop erythroblasts for hemoglobin synthesis and may indeed exert control over the rate of cell proliferation and maturation of the neighboring haemopoietic cells ***(Bollard et al., 2006).***

Haematopoiesis is a two stage process that involve mitotic division or proliferation and maturation or differentiation. Each type of blood cell has parent cells, called stem cells. Haematopoiesis continuous throughout life to replace blood cells that grow old and die, are killed by disease, are lost through bleeding. Medullary hematopoiesis increases in response to proliferative disease, hemolytic anemia, chronic infection and hemorrhage ***(Snell, 2002 , Bullock and Henze, 2000).***

In adult, the extramedullary haematopoiesis (blood cell production in tissue other than bone marrow) is a sign of disease. Extramedullary production of one or more types occurs in disease state that affects erythrocytes e.g., pernicious anemia, sickle cell anemia, thalassemia, hemolytic disease of the new born (erythroblastosis fetalis) and leukocytes (certain leukemias) ***(Farhi et al., 2004).***

Extramedullary haematopoiesis of apparently normal blood cells has been reported to occur in the spleen, liver and less frequently in lymph nodes, adrenal glands, cartilage and kidneys. Stem cells, the progenitor or cells of the haematopoietic system, have the capacity to self replicate as well as differentiate through several different cell development stages into cells that committed to produce either erythrocytes, leukocytes or platelets (figure, 3). The stem cells continue to proliferate until the requisite number mature daughter cells has entered the circulation, the stem cells of lymphocytes and monocyte are stimulated to proliferate and differentiate by other mechanisms, particularly activation of the immune response, but they originate in bone marrow, large numbers of stem cell are produced and stored in the bone marrow ***(Nathan et al., 2003).***

Figure (3): Stem cells in bone marrow



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The stem cells are immature blood cell which can grow into any type of blood cell. They can be obtained directly either from bone marrow or blood. Healthy bone marrow produces the billions of stem cells needed to supply blood cells for the body. When bone marrow fails to function properly or is damaged, it can be restored by stem cell transplantation (SCT) that is transplanted through an intravenous (IV) infusion process similar to blood transfusion. When cells are transplanted, they are carried by the blood into the bone marrow spaces where they implant and multiply, eventually developing into new and healthy cells ***(Farhi et al., 2004).***

Definition of bone marrow transplantation

Bone marrow transplantation (BMT) involves extracting bone marrow containing normal stem cells from healthy donor and transferring it to a recipient whose body cannot manufacture proper quantities of normal blood cells ***(Pamphilon et al., 2009).***

Bone marrow transplantation is a procedure which involves eliminating an individual's haemopoietic and immune system by chemotherapy and/or radiotherapy and replacing it with stem cell (SC) either from another individual or with a

previously harvested portion of the individual's own haemopoietic stem cell ***(King and Hinds, 2003).***

Goals and Indications of bone marrow transplantation:

The goal of a bone marrow transplant is to cure many diseases and types of cancer ***(Daniels and Nosek, 2007).***

The indications for BMT/hematopoietic stem cell transplantation (HSCT) vary according to disease categories and are influenced by factors such as response to prior therapy, pediatric patient's age and performance status, disease status (remission versus relapse) disease specific prognostic factors and available of suitable graft source ***(Gooley et al., 2010).***

However, indications of BMT include the following diseases in pediatric patients; acute lymphocytic leukemia (ALL), acute non lymphocytic leukemia (ANLL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), juvenile chronic myelogenous leukemia (JCML), juvenile myelomonocytic leukemia (JMML), myelodysplasia (MDS), hemophagocytic, Hodgkin's disease (HD), non Hodgkin's disease/lymphoma, retinoblastoma and neuroblastoma (Malignant disorders) ***(Kline, 2006).***In addition to fanconi's anemia, Black Fan-Diamond anemia, thalassemia, sickle cell anemia (SCA), Chediak Higashi syndrome, leukocytic adhesion deficinecy (LAD), congenital dyserythropoietic anemia (CDA), osteopetrosis, niemann pick disease (NPD), mucopolysaccharidosis, Gaucher disease, severe aplastic anemia, severe combined immunodeficiency syndrome (SCID) and Wiskott-Aldrich syndrome (non malignant Disorders) ***(Zaghloul, 2004).***

Types of BMT

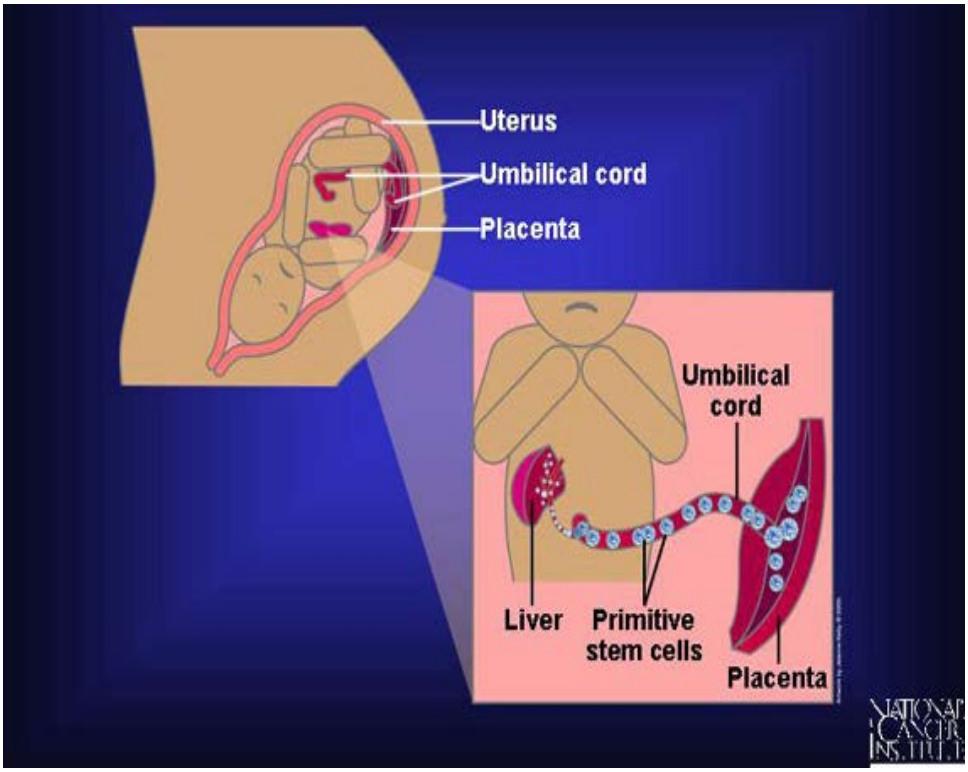
Bone marrow transplants are named according to the donor source as the following:

Allogeneic bone marrow transplantation: Allogeneic BMT refers to transplant between members of the same species in which the donor and recipient are not genotypically identical, usually siblings who are identical with the pediatric patient for the human leukocyte antigen (HLA) ***(Farhi et al., 2004)***.

Syngeneic bone marrow transplantation: A syngeneic BMT is one in which the donor is an identical twin. Where available syngeneic BMT will be the best choice because the twins marrow is histological identical to pediatric patient and make the most histocompatibility, no problem attributable to an immunological barriers ***(Meadows et al., 2001).***

Autologous bone marrow transplantation: The pediatric patient acts as his/her own donor. Autologous BMT refers to the process in which the pediatric patient donate their own bone marrow for using it later in their treatment, autologous marrow is purged to remove malignant cells from the pediatric marrow before the marrow is reinfused. Other sources for BMT under investigation include fetal liver cells, umbilical cord blood (figure, 4), placental blood cells and cadaver transplants ***(Eapen et al ., 2007, Locatelli et al., 2003 and Laughlin, 2001)***.

Figure (4): Cord blood as a source of stem cells.



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Stages of bone marrow transplantation:

The procedure of BMT consists of four stages:

a) Pre transplant evaluation and preparation of pediatric patient and donor.
b) Conditioning regimen.
c) Infusion of the bone marrow cells.
d) Engraftment period ***(Pamphilon et al., 2009).***

a- Pre transplant evaluation and preparation of pediatric patient and donor (appendix, 4):

The pediatric patient during this phase/stage is evaluated or screened for eligibility criteria of transplantation protocols. The factors that determine eligibility include whether the disease is responsive to chemotherapy and/or radiotherapy, the disease stage and the source of stem cells. The pediatric patient also have; an appropriate source of marrow or stem cells, have an adequate venous access, have an adequate financial resource, provide informed consent and educate the pediatric patient/family during this stage about the procedure and the potential complications ***(Bollard et al., 2006).***

The pediatric patients require also comprehensive evaluation to determine the ability to sustain BMT. This stage includes selection of an appropriate marrow donor prior to BMT. It is necessary to match the recipient of the bone marrow with donor to promote a successful transplant. Selection of an appropriate marrow donor is based on blood tests to identify the best suitable donor for recipient. Tests of determine compatibility of marrow consists of: red cell antigen type, ABO and RH histocompatibility. Human leukocyte antigen is used to identify the genetically compatible hematopoietic stem cell donors. The human leukocytic antigens are protein found on the surface of almost all nucleated cells in the body. These antigens regulates the immune response in specific ways and are responsible for the body's ability to recognize self from non-self on a cellular level. Tissue type and the mixed lymphocyte culture (MLC) tests are also performed ***(Fliedner, 2002).***

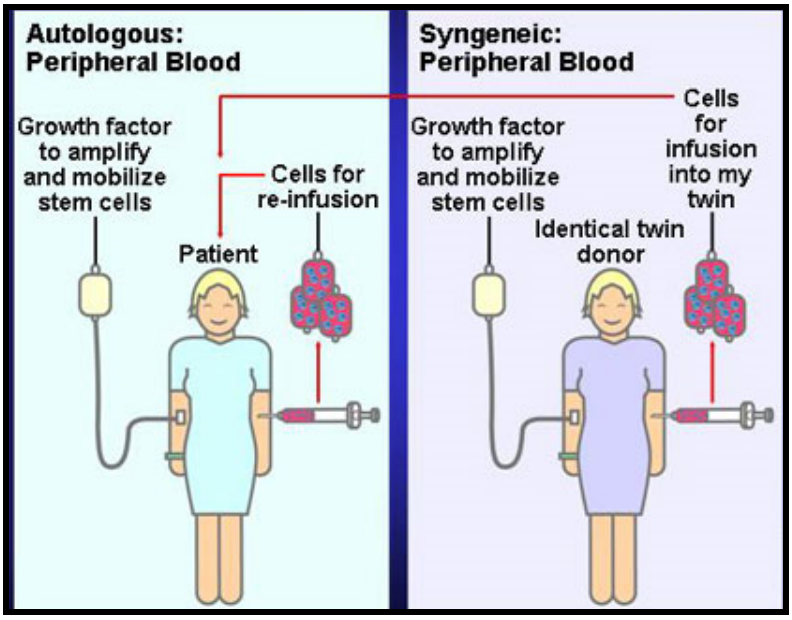
A family conference/meeting is scheduled to obtain information consent, discuss the risk of transplant related morbidity and mortality and the expected outcomes with pediatric patient/family and admission of the pediatric patients at the hospital/BMT unit. The pediatric patient comes into the BMT up to 10-17 days before transplant for dehydration and placement of the central venous catheter. The blood products, bone marrow and medications will be administered through the central venous catheter ***(Oliansky et al., 2007 and Rizzo et al., 2006).***

The pediatric patient is placed in a protective isolated room, where the use of the laminar air flow (LAF) rooms to decrease infection related morbidity and mortality. Orientation of the pediatric patient/family with BMTunit. After the pediatric patient is admitted to the BMT unit, the nurse performs a thorough physical assessment, an evaluation of psychological, social background, coping states and initiates an individualized care plan. The pediatric patients must undergo decontamination of their gastrointestinal tracts, skin and body cavities (from isolation till engraftment) ***(Adams et al., 2004).***

Haematopoietic stem cell collection from the donor (in allogeneic transplant) and pediatric patient (in autologous transplant) using either peripheral blood stem cell collection or bone marrow harvesting/aspiration according to **Kline, (2006)** as the following:

1- Peripheral blood stem cell collection is the most commonly used which include the following, donor or pediatric patient use of hematopoietic growth factors granulocyte colony stimulating factor (G-CSF)/neupogen subcutaneous once daily after complete blood count performed (figure, 5) ***(Bollard et al., 2006)***

Figure (5): Preparing patients for autologous/syngeneic transplants.



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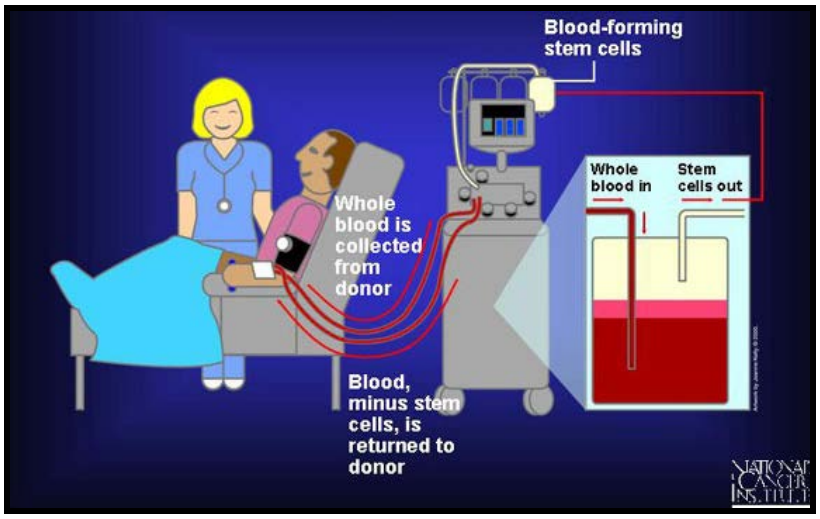
The G-CSF given with or without chemotherapy to release marrow stem cells into the peripheral blood, which collected from the veins/central venous catheter subclavian of the donor/pediatric patient ***(Hobbs, 2011)***.

The process of collecting stem cells from circulatory blood is termed apheresis (figure, 6). The pediatric patient/donor attaching to the apheresis machine which withdraws blood via a large bore central venous catheter. The blood is collected, the stem cells are separated out and the remaining platelets and red blood cells are then reinfused back into donor/pediatric patient. Apheresis takes two to four days. The donor /pediatric patient is observed for symptoms of hypocalcaemia as perioral tingling ***(Chernecky and Berger, 2008).***

Figure (6): Apheresis: harvesting stem cells from peripheral blood.



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2- Bone marrow harvesting or aspiration from donor and pediatric patient. The procedure of BMT aspiration is used to assess and diagnos most blood dyscrasis. Examination of the marrow cells reveals the types, numbers, maturation level, size and composition of tissue to establish the diagnosis and determine protocols. The sites for aspiration of bone marrow in donors/ pediatric patients **(appendix, 7)** are anterior or posterior iliac crest (in young children), the sternum used in old children (6-12 years) but shouldn't be used in young children (3-6 years) because it is an unfused fragile bone marrow in close proximity to vital organs. Aspiration from the anterior tibia tuberosity in neonates and infants because the active haematopoiesis occurs in long bone ***(Azar et al., 2003 and Coop, 2001).***

Bone marrow aspiration is carried out under sterile conditions in operating room utilizing general anesthesia. The pediatric patient/donor is placed in prone position and slightly flexed at the waist. The volume of each aspiration should be 10 to 15 ml or less to minimize the amount of hemodilution and blood contamination. The amount of bone marrow aspirated depends on the donor/pediatric patient weight and the concentration of cells in donated marrow. This is obtained by aspirating 10-20 cm bone marrow per kilogram of recipient weight. The side effects of marrow aspiration are pain, bleeding at puncture site, lower back pain, nausea, vomiting,

hypotension, sore throat, fever and anemia ***(Foucar, 2003).***Then the marrow is placed in a beaker containing tissue culture medium and preservative free heparin, while the filtered marrow is placed in a standard transfusion bag and administer to the recipient intravenously, through a central venous access device (Hickman catheter) or preserved and stored for future use. In the latter case, which occurs only with autologous BMT, the harvested marrow treated before cryopreservation to eliminate any occult tumor cells that may be present. The marrow is preservative frozen stored in solution with Dimethyl sulphoxid (DMSO) ***(Burt et al., 2008)***.

b) Conditioning regimen:

Conditioning regimen involves the administration of conditioning or preparative regimen. Conditioning regimens consists of high dose of chemotherapy with or without total body irradiation. Regimen selection is determined by the underlying disease and type of stem cell transplantation. The purpose of conditioning regimen is to immunosuppress the pediatric patient, which decrease the risk of graft rejection, eradicate any residual malignant cells and create space in the bone marrow cavities to allow engraftment of donor cell ***(Alyea et al., 2006).***

According to ***Korthof et al., (2005)***, there is no specific conditioning protocol to be administered to all pediatric patients. However, the conditioning regimens will vary according to disease states, type of treatment and age of child. Children under two years of age shouldn't receive total body irradiation (TBI) because cranial radiation for long term will affect cognitive, growth and development of the pediatric patients. While children over two years of age, the conditioning regimen will consists of either high dose of chemotherapy alone or in combination with total body irradiation or administer medications instead of radiotherapy according to diagnosis of the child and conditioning regimen protocol. In Day -1 pre BMT, sandimmune or cyclosporine is administered for the pediatric patient in case of allogeneic and syngeneic BMT type only. In day 0 bone marrow infusion/transplant administered for the pediatric patient ***(Timby and Smith, 2003).***