

Guide to Pediatric Stem Cell Transplantation

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I. INTRODUCTION

The purpose of the Pediatric Bone Marrow Stem Cell Manual is to present, in a clear and succinct fashion, general and specific topics encountered routinely while taking care of bone marrow transplant patients.

The Manual should serve as a guide to stimulate critical thinking and provide insight about problems in the management of bone marrow transplant patients.

The manual contains an initial section where the indications and rationale for Bone Marrow Transplantation are presented. This is followed by a brief review of the routine evaluation prior to bone marrow transplantation, the selection of donors and technique of bone marrow harvesting, the preparative regimens and prophylaxis for infections and graft versus host disease. The next sections address general topics in the management of patients using a "systems" approach.

A. INDICATIONS AND RATIONALE FOR BONE MARROW TRANSPLANTATION

Bone marrow transplant (BMT) is the treatment of choice for numerous childhood diseases. In many of them, the mortality is virtually 100%, with no adequate or acceptable alternative therapy of curative intent. There are three rationales for a BMT. The first and easiest to appreciate is the replacement of defective bone marrow stem cells with normal functioning cells from a healthy marrow donor. For children with SCID, the lymphocyte is the defective cell. In beta-thalassemia the erythroid cell population is abnormal, in chronic granulomatous disease and Chediak-Higashi Syndrome the myeloid cells are defective, and in severe aplastic anemia both the myeloid and erythroid marrow cells are affected and often must be replaced in order to obtain a cure.

The second disease category in which there is an obvious rationale for BMT is malignancy. Much of our understanding of the immunobiology and genetics of marrow transplantation comes from studies in patients with acute or chronic leukemia. The primary rationale for a BMT in malignancy is to "rescue" the marrow. A BMT allows the administration of doses of chemotherapy and total body irradiation (TBI) that maximizes the killing of cancer cells, but which also ablates the normal bone marrow stem cells. The BMT replaces the ablated recipient marrow with healthy normal functioning marrow. A secondary rationale which in some malignancies may be quite important has been termed graft versus tumor or graft versus leukemia. There is evidence to suggest that the donor marrow (the donor immune system) may play a significant role in at least some malignancies, particularly in chronic myelocytic leukemia (CML), in reducing the recurrence rate. For children with acute lymphocytic leukemia (ALL) in 2nd remission, acute nonlymphocytic leukemia (ANLL) also called AML – acute myelocytic leukemia) in 1st (if high-risk AML) or 2nd remission and chronic myelogenous leukemia (CML) in advanced phase, the long term disease free survival with conventional chemotherapy remains poor so that BMT is the treatment of choice. More recently, autologous stem cell transplantation has been added to the therapeutic regimens for certain solid tumors, of which high risk neuroblastoma in children has been best evaluated.

The third disease category in which BMT has been used is the inborn errors of metabolism in which there is a generalized genetic defect with systemic clinical symptomatology. In many of these diseases, the mechanism for tissue damage is a build-up of toxic metabolites. The rationale for a BMT is that tissue histiocytes originating in the donor bone marrow repopulate the "affected" organs, remove toxic metabolites and eliminate or reverse organ damage. BMT for inborn errors of metabolism remains a controversial area of clinical research. The largest experience is in children with type I mucopolysaccharidosis (Hurler syndrome). This disorder affects multiple organs including the central nervous system (CNS). Most children with Hurler syndrome who have received transplants have had pre-existing CNS disease. At least one group has been followed for several years post transplant, indicating that survival can be significantly prolonged by a BMT, that the CNS damage does not seem to be reversible, but that the progressive CNS deterioration that occurs in the natural history of this disorder appears to be halted. This suggests that even in some inborn errors, which involve the CNS, transplantation may be efficacious if performed sufficiently early, prior to significant damage.

TABLE I

Non-Neoplastic Diseases Successfully treated by allogeneic BMT

IMMUNODEFICIENCY DISEASES

Severe combined immunodeficiency syndrome
Wiskott-Aldrich syndrome
Chediak-Higashi syndrome
DiGeorge's syndrome
Reticular dysgenesis
Congenital agranulocytosis
Cartilage-hair hypoplasia syndrome

HEMATOLOGIC DISEASES

Aplastic anemia
Fanconi's anemia
Blackfan-Diamond syndrome
Beta-thalassemia major
Sickle cell anemia
Neutrophil actin dysfunction
Chronic granulomatous disease
Megakaryocytic thrombocytopenia
Thrombocytopenia-absent radius syndrome

GENETIC DISEASES

Infantile osteopetrosis
Mucopolysaccharidoses
Gaucher's disease
Metachromatic leukodystrophy
Adrenoleukodystrophy
Lesch-Nyhan syndrome
Generalized glycogenosis

TABLE 2

 Neoplastic Diseases successfully treated by BMT

Acute leukemias
 Chronic myelogenous leukemia
 Preleukemia and acute myelofibrosis
 Langerhan's cell histiocytosis
 Lymphomas
 Other solid tumors
 Neuroblastoma
 Ewing's Sarcoma
 Rhabdomyosarcoma
 Primitive neuroectodermal tumor
 Osteosarcoma
 Glioma

TABLE 3

 Types of Bone Marrow Transplants

type of graft	source of Bone Marrow
Allogeneic	related donor (usually a sibling) unrelated volunteer donor unrelated umbilical cord blood
Syngeneic	identical twin
Autologous	patient

In summary, bone marrow transplantation can be curative for several non-malignant diseases such as: Immunodeficiency, Hematologic and Genetic diseases (table 1). In most of these diseases, successful treatment involves the replacement of abnormal bone marrow cells with normally functioning bone marrow cells. In others, it involves the replacement of missing or defective enzymes that prevent tissue or organ damage. In malignant diseases (table 2), bone marrow transplantation allows the maximization of chemotherapy and radiotherapy to eradicate malignant cells, this also leads to bone marrow ablation, thus requiring a bone marrow transplant to "rescue" the ablated marrow plus allowing for a potentially beneficial immunologic benefit as well.

Types of Bone Marrow Transplantation

There are three general categories of BMT based on the type of marrow donor: syngeneic, allogeneic and autologous (table 3). For the occasional patient, the ideal donor (typically not for the cancer patient and not for patients with genetic diseases) is the identical twin who is syngeneic with the recipient. For children with cancer a syngeneic marrow reduces some of the potential complications of a BMT such as marrow rejection and graft versus host disease but this type of transplant is usually not indicated because there is also a higher risk of leukemic relapse

in recipients of syngeneic marrow presumably secondary to a loss of the before mentioned graft vs. leukemia effect.

An allogeneic transplant is one in which another donor either related or unrelated is used as the stem cell source. An allogeneic BMT may be used for any disease category in which a transplant is indicated. The most common allogeneic donor is a histocompatible related sibling. The human leukocyte or histocompatibility antigens (HLA) are coded for by three major genetic loci located on the short arm of chromosome 6. There are hundreds of HLA antigens but we test for only the 6 (sometimes 10) that are most involved with host-donor interactions. The 6 antigens tested are: two A antigens, two B antigens and two D/Dr antigens. Each set of three HLA antigens (A,B,D/Dr) inherited from each parent are called a haplotype. Every individual inherits one maternal and one paternal HLA haplotype. Thus, there is a 25% chance that any sibling will have inherited the same two haplotypes, that is, being histocompatible or HLA matched with the patient. There are multiple alleles, which are expressed at each genetic locus. Thus, it is extremely unlikely (1:300,000) that any two unrelated individuals will be matched for all six HLA antigens. The chance of a parent being HLA compatible with a child is <1:10. Thus, most related histocompatible BMT involve sibling donors.

The other types of allogeneic donors are either HLA matched unrelated individuals or umbilical cord blood or mismatched related donors.

An autologous BMT utilizes the patients own BM or PB stem cells as a rescue from the high-dose therapy given to cure their underlying disease.

B. EVALUATION FOR BONE MARROW TRANSPLANT

Extensive discussion with the patient, their family and the referring physician regarding the indications and rationale for bone marrow transplantation take place. There is a careful review of the risks and benefits of bone marrow transplantation.

The patient's medical history is reviewed in detail. A complete evaluation should include:

1. Diagnosis.
2. Tumor staging in malignancy.
3. Past and present treatment.
4. Complications secondary to treatment.
5. Medical and surgical problems.
6. Evaluation of past infections, present infections and potential reactivation of infectious diseases.
7. History of allergies.
8. Transfusion history.
9. Psychosocial assessment.
10. HLA typing of parents, siblings and patient, including a donor search for patients without a family match.
11. ABO typing and evaluation of the allosensitization status of the patient
12. Determination of a marker for allogeneic bone marrow transplant to ensure evaluation for donor cell engraftment.
13. Evaluation of body systems: cardiac, respiratory, renal, endocrine and hepatic.

C. BONE MARROW HARVESTING AND PROCESSING

Technique of Bone Marrow Collection

The bone marrow donor is taken to the operating room, where under general anesthesia, the bone marrow is obtained by multiple aspirations of both posterior iliac crests. Several aspirations are done through the same needle hole and different areas of the bone marrow are sampled. The volume aspirated should be limited to about 5 cc since any additional volume will dilute the nucleated bone marrow cells with peripheral blood. The goal is to obtain about 300 million nucleated bone marrow cells per kilogram of the recipient's body weight to assure satisfactory engraftment. The older the donor, the lesser the number of nucleated bone marrow cells per volume of aspirated marrow. Nucleated bone marrow cell counts obtained during collection can help determine the volume of bone marrow aspirate needed.

As the marrow is being collected, it is pooled in a sterile container with culture medium and heparin. Once the bone marrow is pooled it is filtered through stainless steel mesh screens to remove bone spicules, clotted material, and fat. After this step, the bone marrow is ready to be placed in a sterile container. The container can be a blood transfer pack used to transfuse the patient, or a sterile container where the marrow can be stored for cryopreservation in liquid nitrogen or handled for processing in the laboratory.

Bone Marrow Processing

There are several techniques for ex-vivo processing of bone marrow and there is a specific indication and rationale for each technique. First, in the setting of malignancy, when autologous marrow is used, tumor cell purging with chemotherapy, immunologic or physical techniques may be done to eliminate neoplastic cells and reduce the incidence of recurrent disease. Typically with auto transplantation peripheral blood stem cells (PBSCs) are used and not bone marrow. These are collected by apheresis usually following cell count recovery after chemotherapy or after G-CSF mobilization. Second, to reduce the risk of graft versus host disease associated with allogeneic BMT one can deplete the donor marrow of T-cells, again this can be achieved with immunologic and physical techniques such as monoclonal antibodies or soybean agglutination. Third, in the case of an ABO incompatible transplant, the red blood cells are removed to prevent isohemagglutinin-mediated hemolysis.

D. PREPARATIVE REGIMENS

The purpose of the preparative regimen is to condition the recipient for bone marrow transplantation. First, it must provide immunosuppression in order to prevent the host from rejecting the donor marrow. Second, the marrow must be physically ablated to allow room for the donor marrow to settle and proliferate. And third, in malignant disease the preparative regimen should eradicate malignant cells.

TABLE 4

Preparative Regimen Agents

AGENTS USED PRIMARILY FOR IMMUNOSUPPRESSION

Anti-thymocyte globulin
Fludarabine

AGENTS USED PRIMARILY FOR ANTINEOPLASTIC EFFECTS

Busulfan
Ara-C
VP-16
Melphalan
Carboplatin
BCNU
Thiotepa

AGENTS USED FOR BOTH PURPOSES

Total body irradiation (TBI)
Cyclophosphamide

Suppression of the recipient's immunologic resistance is necessary to prevent host versus graft reaction, which interferes with engraftment of the donor cells.

The degree of immunosuppression required will depend on several factors. These include the degree of underlying immunosuppression from the primary disease and its therapy, sensitization from prior blood transfusions, the degree of histocompatibility, and the number and type of bone marrow cells infused.

In certain diseases the degree of immunosuppression produced by the disease and its treatment may be such that the conditioning regimen requires less immunosuppression. Prior blood transfusions may sensitize the patient against non-HLA histocompatibility determinants. As transplants are carried out with a progressive degree of histoincompatibility more immunosuppression for sustained engraftment is needed. Removing T-cells from the donor marrow reduces the risk of graft versus host disease, but may require additional immunosuppression to reduce the risk of graft failure

Commonly used agents in Preparative Regimens

There are numerous agents in use which can be classified according to their immunosuppressive and antineoplastic effect (table 4).

Total body irradiation (TBI) with x-rays or gamma rays is an effective agent for conditioning. It is very advantageous in the case of leukemia where it lacks cross-resistance to chemotherapeutic drugs, it can treat pharmacologic sanctuaries and it provides potent immunosuppression. With doses above 1,000 cGy it usually produces permanent marrow ablation. TBI is fractionated/hyperfractionated over several days to increase the maximal tolerated dose; this reduces the toxicity to normal tissues but not its antileukemic effect. In addition, shielding is used to reduce the level of radiation to specific areas of the body such as

the lungs. The major drawback of this useful agent is its multiple side effects such as acute fluid shifts, fever, mucositis, nausea, fatigue and diarrhea. TBI acts as both an immunosuppressive and antineoplastic agent, while most other agents have one predominant effect.

Antithymocyte globulin (ATG) is an agent used primarily for its immunosuppressive effect; its toxic effects include: fever, chills, rash and anaphylaxis. Cyclophosphamide is another immunosuppressive agent, which produces stable engraftment with a low rate of rejection. It has well known side effects such as hemorrhagic cystitis, cardiotoxicity, and SIADH.

Busulfan is an agent used primarily for its antineoplastic effect. It has anti-hematopoietic stem cell activity and it has been successfully utilized in the preparation of patients with AML. Its well known side effects include nausea, seizures, alopecia and pulmonary fibrosis. Cytosine arabinoside (ARA-C) is another antineoplastic agent useful in lymphoid malignancies. Its side effects include: fever, mucositis, nausea, diarrhea, rash, conjunctivitis and cerebellar dysfunction. Finally, Etoposide (VP-16) is an almost exclusively marrow toxic agent with proven activity against malignant cells. It is able to penetrate the CNS after high intravenous doses.

Most preparative regimens for allogeneic transplants have combined high-dose cyclophosphamide and total-body irradiation. Many other combinations of agents described above have been used to provide better antitumor effect, decreased relapse rate, and less extramedullary toxicity. In addition, multi-drug chemotherapy has been used as an alternative to total body irradiation. For example, the combination of busulfan and cyclophosphamide has been used successfully for treating myeloid disease.

TBI and chemotherapy used in the preparative regimen can be toxic to several organ systems. The most susceptible are the bone marrow and the gastrointestinal tract. However, the CNS, heart, lungs, and liver may also be affected and in the most severe circumstances result in irreversible organ failure and death. Several factors play a role in determining the susceptibility of the patient to the preparative regimen: age, prior chemotherapy or radiation therapy, history of prior infections. For most of these toxic reactions, it appears that young children have a lower incidence than older children and adults.

Other acute effects of the preparative regimen include nausea, vomiting, diarrhea, mucositis, alopecia, hemorrhage and infection (table 5). Chronic side effects include those involving intellectual development, growth, sexual maturation, and an increased risk of second malignancies.

TABLE 5

Preparative regimen complications

Pancytopenia
Mucositis and other oral complications
Gastroenteritis and diarrhea
Urotoxicity
Hepatic damage
Cutaneous toxicity
Neurotoxicity
Cardiotoxicity
Interstitial pneumonitis
Fluid and electrolyte imbalance

In summary, there are many preparative regimens. They all have a marginal therapeutic index. Any increase in toxicity, however slight, may produce an unacceptable increase in

overall toxicity and negate any improvement in disease free survival. As we learn more about the immunobiological aspects of bone marrow transplantation and cancer, better preparative regimens will be designed.

E. INFECTION PROPHYLAXIS

After bone marrow transplantation (particularly allogeneic) there are patterns of infectious complications that are related to the immunobiology of transplantation. Immune reconstitution post transplant follows a general pattern developing from immature to mature immune functions. Immune reactivity during the first month after transplant is low. Cytotoxic and phagocytic functions recover by day 100, while more specialized and cooperative functions of T and B cells remain impaired up to one year or more post grafting. After the first year post grafting, the various components of the immune system of most healthy marrow recipients begin to work synchronously, whereas the immune systems of recipients with chronic graft versus host disease remain crippled.

These infections are usually predictable in their character and expression. Early on, the preparative regimen generates complete aplasia, which can be associated with severe and life-threatening bacterial infections, predominantly with gram-negative organisms derived from the bowel flora and gram-positive organisms derived from the skin flora. In the early aplastic phase viral infections are not common. Systemic infections with invasive fungi less common but are a big problem when there is prolonged aplasia or in patients whose immune systems are severely compromised by graft-versus-host disease (GVHD) or its treatment.

Once marrow recovery is achieved, systemic infections will generally disappear unless acute host versus graft disease develops. This complication will impair the skin and gastrointestinal barrier and all systemic defense mechanisms. This can lead to polymicrobial infections and set the stage for life-threatening viral or fungal infections.

With recovery of cellular and humoral immune function in the first and second year after transplant, patients are likely to develop sinopulmonary infections primarily with encapsulated gram-positive organisms. At this time, the patient is at risk of developing chronic graft versus host disease and associated functional hyposplenism, which further predisposes to infections with encapsulated organisms. However, any of these infections can occur in the absence of chronic graft versus host disease, and are associated with an IgG2 and IgG4 subclass deficiency.

Infections are a major cause of morbidity and mortality in the bone marrow transplant patient. By understanding the kinetics of immune system recovery and the factors that predispose to infection, strategies to prevent morbidity and mortality due to infections have been developed:

1. Gnotobiosis in protective environments: Washing with antimicrobial solutions to decontaminate the skin. Placing the patient in isolation in a room with a high efficiency particulate air filter and laminar air flow. Gastrointestinal tract decontamination with oral non-absorbable antibiotics such as Vancomycin and Gentamycin. Very few BMT centers use this form of environment since it has not been proven necessary.
2. Introduction of less toxic preparative regimens to prevent skin and gastrointestinal tract breakdown.
3. Passive serotherapy with intravenous gamma globulin.

4. Use of antibacterial and antiviral agents such as: Septra, penicillin, quinolones, etc. for bacterial infection prophylaxis. Oral/topical mouth care with Nystatin and Clotrimazole troches. Acyclovir to prevent Herpes Simplex virus infections.
5. Effective prevention of graft versus host disease with Cyclosporine, Methotrexate and Prednisone.

F. GRAFT VERSUS HOST DISEASE

Graft versus host disease (GVHD) is a major cause of morbidity and mortality after allogeneic BMT. GVHD occurs in 25% to 70% of patients with HLA-matched transplants, depending on whether or not a related family member or unrelated stem cell source is used. GVHD includes two syndromes, acute and chronic GVHD. They differ in time of onset, organ involvement, rate of progression and response to therapy.

ACUTE GVHD

Acute GVHD occurs within the first 100 days following BMT and is associated with a skin rash, hepatic dysfunction and diarrhea. Cutaneous manifestations of acute GVHD are very common and often begin as a maculopapular rash often and, if untreated, may progress to form bullae resembling scalded-skin syndrome. Sometimes mild skin rashes resolve without therapy. Histologically, a sparse lymphocytic infiltrate, basilar vacuolization, single-cell necrosis, and in severe cases, separation at the dermal-epidermal junction can be seen.

The gastrointestinal tract is frequently involved in acute GVHD, with diarrhea being the most common symptom. Severe cases often have large volumes of diarrhea per day and associated crampy abdominal pain. Rectal biopsy is often helpful in distinguishing acute GVHD from gastrointestinal tract damage associated with irradiation or infection. Histologic changes include single-cell necrosis, crypt drop-out, and mucosal ulcerations.

Another target organ in acute GVHD is the liver. Elevated hepatocellular and are commonly seen. Histologically, varying degrees of hepatocellular necrosis is seen. Involvement of the portal tract is common with varying degrees of hepatocellular necrosis, and degrees of damaged bile duct epithelium ranging from single-cell necrosis to complete obliteration of bile duct epithelium. Lymphoid infiltrates in the portal tract are also common. There is evidence supporting the role of immune mechanisms, particularly T lymphocytes in the pathogenesis of GVHD.

CHRONIC GRAFT VERSUS HOST DISEASE

Most patients will have had preceding acute GVHD. Symptoms can develop as a progressive extension of acute GVHD or following a quiescent period after resolution of acute GVHD. Some patients will have a de novo late onset of GVHD, without evidence of prior acute GVHD.

The spectrum of clinical symptoms in patients with chronic GVHD resembles several known collagen vascular diseases. Specific clinical manifestations are as follows:

Skin: Early symptoms may include dryness, itching and loss of sweating while late symptoms are those of tightness and contracture. The onset of symptoms usually is more gradual, and preferentially occurs in sun exposed areas.

Mouth: The most frequent symptoms are pain and dryness of the mucous membranes. Xerostomia may facilitate development of dental caries. White plaques may develop.

Eyes: Ocular involvement is observed in up to 80% of patients. Most of the symptoms develop secondary to insufficient tear production as part of the sicca syndrome. Ocular sicca can lead to keratitis and scarring. The long-term use of corticosteroids and total body irradiation can cause ocular problems, in particular cataract formation. The sicca syndrome can also involve the mouth, the genital tract, in particular vagina, and the mucosa of the tracheobronchial tree.

Specific clinical manifestations involving the gastrointestinal tract:

Esophagus: Intestinal involvement is less common in chronic GVHD. The esophagus is most often affected. It can present as dysphagia, pain, swelling or retrosternal pain. Web formation can occur associated with mucosal desquamation, strictures and partial occlusion along with functional abnormalities. Dysphagia may lead to poor caloric intake and weight loss. Esophageal obstruction can also cause aspiration and subsequent recurrent pulmonary disease.

Liver: About 90% of patients with chronic GVHD have various degrees of chronic liver disease. When it is associated with skin manifestations only, the outcome is usually more favorable than in patients with extensive chronic GVHD.

Gut: Stomach and gut are rarely affected by chronic GVHD.

Other areas of involvement or specific problems in chronic GVHD include:

Vagina: Chronic GVHD may cause inflammation, sicca, adhesion and stenosis of the vagina. If atrophy is the most likely cause, dilators and estrogen creams are recommended. Systemic immunosuppressive treatment and in some cases surgical intervention may be required.

Serosal involvement: Some degree of involvement is encountered in about 20% of patients with extensive chronic GVHD. Symptoms are secondary to pericardial, pleural and synovial effusions.

Lung: Obstructive lung disease has been increasingly recognized as a late manifestation of chronic GVHD. About 5-10% of long-term survivors with chronic GVHD may ultimately develop this type of complication.

Myasthenia gravis: Few patients have been described. The manifestation of the disease is suspected to be related to immune dysregulation and donor-host alloreactivity. Other rare neuromuscular abnormalities in chronic GVHD may include polymyositis and peripheral neuropathy.

Autoimmune problems: The clinical manifestations of chronic GVHD resemble those of some spontaneous autoimmune diseases. Some patients with GVHD may develop antiplatelet antibodies and autoimmune thrombocytopenia.

Immunodeficiency: Patients have delayed immune recovery and remain immunodeficient usually as long as the disease is active. In addition, patients often have a deficiency of intestinal secretory immunity and a reduced level of salivary IgA. This secretory IgA deficiency may contribute to the frequent sinobronchial infections. Additionally pats. are typically

Infectious complications: The immunologic disorders predispose patients to late infections, mostly with encapsulated bacteria. There is some uncertainty about the best method of infection prophylaxis.

GVHD is the major limitation in the use of BMT for patients without a matched donor. The successful prevention and treatment of GVHD would greatly improve the outcome of patients after BMT.

Two approaches have been used to prevent GVHD. The first and most widely used involves administration of immunosuppressive agents such as methotrexate, prednisone, antithymocyte globulin, cyclosporine or FK506 (Tacrolimus) following BMT (table 6). Several combinations of these drugs are used. The second approach involves elimination of T lymphocytes from the donor marrow prior to BMT.

TABLE 6

Agents used in GVHD prophylaxis

PRETREATMENT OF DONOR MARROW TO REMOVE T LYMPHOCYTES

Monoclonal anti-T cells antibodies and complement

Immunotoxin conjugates

Fractionation with soybean lectin agglutination and resetting with sheep erythrocytes.

High dose corticosteroids

Counterflow centrifugal elutriation

Positive stem cell (CD34+ cells) selection

POST-TRANSPLANT TREATMENT

Low-dose methotrexate

Corticosteroids

Antithymocyte globulin

Cyclosporine

FK506

Cellcept (Mycophenolate Mofetil or MMF)

The immunosuppressive agents used are given in an attempt to suppress the immunoreactivity of donor-derived cytotoxic T cells against recipient target organs, and thus to induce a state of immunologic "tolerance" of the engrafted lymphocytes to the recipient antigens. However, the disadvantage of most of these agents is their lack of specific activity against cytotoxic T cells. Instead, these agents cause broad-spectrum immunosuppression that can impair satisfactory immunologic reconstitution after BMT.

Cyclosporine is a potent immunosuppressive agent for the prophylaxis and treatment of acute GVHD. Cyclosporine is especially effective when combined with other agents such as corticosteroids or methotrexate. Although it suppresses the development of donor cytotoxic T cells it does not affect the proliferation of suppressor T cell populations. Thus, use of this drug facilitates immunological tolerance of graft to host. Cyclosporine had led to decreased incidence of acute GVHD, improved survival in recipients of allogeneic BMT, and is devoid of toxicity to the recovering marrow. However, this drug can impair renal function and, rarely, may produce reversible acute renal failure. It also causes fluid retention, hypertension (particularly when combined with steroids), and hirsutism.

Infants and young children have a more rapid systemic clearance and a larger steady-state distribution of cyclosporine, thus they may require higher doses to maintain adequate levels of

the drug. Allogeneic BMT recipients are given prophylaxis with the drug for only 6 to 12 months, after which it is generally discontinued because a state of tolerance of donor lymphocytes to host is attained.

Another strategy to prevent acute GVHD is the depletion of lymphocytes from the allogeneic marrow graft before infusion into the recipient, however, both failure of sustained engraftment and increased relapse rates have been reported in recipients of T cell-depleted marrow grafts. In many instances, these problems have negated the potential benefits of reducing morbidity and mortality related to GVHD.

II. GENERAL TOPICS IN THE MANAGEMENT OF PEDIATRIC BONE MARROW TRANSPLANT

A. FLUID, ELECTROLYTE AND NUTRITION MANAGEMENT

Introduction

All transplant patients receive large quantities of intravenous fluids from medications and total parenteral nutrition (TPN). Several complications secondary to the conditioning regimens and medications cause generic and specific fluid and electrolyte problems soon after transplantation. Careful monitoring and prompt intervention will allow caregivers to prevent and quickly correct most of these problems. The goal of nutritional support in bone marrow transplantation is that of nutritional repletion or maintenance of nutritional status. Nutritional repletion may be required in patients who have undergone multiple courses of aggressive chemotherapy and have persistent problems with oral intake, and enter the transplantation process in poor nutritional status. Other patients may be well nourished prior to transplantation, but the toxic preparative regimens used may cause mucositis, esophagitis, anorexia and enteritis and these patients will require TPN to maintain their nutritional status.

Fluids

Complications are usually secondary to prior chemotherapy or the preparative regimen. For example, the use of Cytoxan requires vigorous hydration and diuresis to prevent accumulation of its toxic metabolite, acrolein, in the bladder.

Total body irradiation may predispose to capillary leak syndrome, which causes edema and "third spacing".

Cytosin can also cause acute water retention with secondary hyponatremia and hypotonicity by causing SIADH. This syndrome should be considered whenever the patient's urine output is decreased concomitant with the infusion of Cytosin especially associate with decreasing serum Na. A lower urine osmolarity than serum osmolarity at the time is diagnostic but is rarely necessary to perform. The therapy for Cytosin induced SIADH is never fluid restriction but aggressive diuresis.

In summary, fluid therapy should be evaluated daily by assessing any risk factors for complications, and by careful monitoring of the patient's twice daily body weight, as well as careful assessment of intake and output.

Electrolytes and Minerals

Most electrolyte problems are those commonly seen with the use of intravenous fluid and total parenteral nutrition. Again, the key to management is careful monitoring. Electrolyte imbalance may also occur secondary to fluid shifts, vomiting and diarrhea.

Chemotherapy and antibiotic therapy may compromise renal glomerular and tubular functions and electrolyte and mineral homeostasis, Cisplatin nephropathy can cause renal magnesium and potassium wasting. Amphotericin B can cause renal tubular acidosis and also induce potassium and magnesium wasting. Cyclosporine is also commonly associated with electrolyte wasting and in particular magnesium and phosphorus. As a result both oral and IV supplementation is the routine.

Nutrition

Bone marrow transplant is associated with several complications such as anorexia, fever, nausea, vomiting, mucositis and diarrhea. These complications are detrimental to the nutritional status of the patient requiring enteral feeds or more commonly, TPN. The patient's nutritional status should be continuously reevaluated in order to initiate oral feedings as soon as possible, and to avoid the complications associated with parenteral nutrition.

B. RESPIRATORY COMPLICATIONS AND MANAGEMENT

The most common immediate complications with bone marrow transplantation may occur with administration of the donor bone marrow. There is a risk of developing respiratory distress secondary to: pulmonary edema from excess fluid; a shower of pulmonary emboli to the lung capillary bed if the donor marrow was not filtered appropriately; and lastly allergic reactions or anaphylaxis to preservatives added to the donor marrow if it was processed or stored. In the case of autologous stem cell infusion, the cryoprotectant DMSO is also associated with acute pulmonary distress.

Other acute pulmonary toxicity early after transplantation is associated with chemoradiotherapy and it is manifested as interstitial pneumonitis. Interstitial pneumonitis can be secondary to infections (usually viral), irradiation, drugs (e.g., Cytosan, busulfan and methotrexate) and idiopathic. Interstitial pneumonitis can occur as early as one week and as late as two years after transplant, however its peak is at approximately 8 to 10 weeks after transplant.

Bacterial and fungal infections can occur at any time, but with recovery post-engraftment they become less common. In patients who develop chronic graft-versus-host disease pulmonary infections can occur as a delayed problem.

Late pulmonary complications of bone marrow transplant can be restrictive or obstructive in nature, and are commonly associated with chronic graft versus host disease.

All respiratory system complications present with similar symptom complexes, and with different degrees of severity depending on the seriousness of the problem:

1. RESPIRATORY DISTRESS

This symptom may occur in the setting of pulmonary edema, pulmonary infection, interstitial pneumonitis, fever, anemia, acidosis, pleural effusion, sepsis, pulmonary embolus and impending shock.

2. COUGH

This symptom may occur in the setting of pulmonary infection, pulmonary edema, upper respiratory tract infection (sinusitis), congestive heart failure, and pulmonary embolus.

3. HEMOPTYSIS

This sign may occur in the setting of epistaxis, fungal pneumonia, pulmonary hemorrhage and pulmonary embolus.

4. CHEST PAIN

This symptom may occur in the setting of pulmonary infection, cough, Herpes Zoster and pulmonary embolus.

5. FEVER

This sign usually occurs in the setting of infection typically in conjunction with some other respiratory sign or symptom.

Complications

1. Pulmonary edema: May develop early after transplantation, in the setting of generalized capillary leak syndrome or veno-occlusive disease with a significant increase in body weight. One must proceed to evaluate this with a chest x-ray, monitor oxygen saturation, and arterial blood gas if respiratory distress is severe. Evaluate cardiovascular status, An aggressive trial with diuretics should be started. Reevaluate the patient's fluid intake. Pulmonary edema should respond to diuretic therapy, if this does not occur, another diagnosis should be considered.
2. Pulmonary Emboli: A shower of microemboli to the lung capillary bed may occur with marrow transplantation. During marrow harvesting steps are taken to avoid this complication by filtering the marrow through stainless steel mesh screens.
3. Pulmonary infection: The patients are at risk for bacterial or fungal infections due to immunosuppression. Infections should present with fever and other respiratory symptoms. In the setting of fever and neutropenia, the patient will be started on broad-spectrum antibiotics after appropriate cultures are obtained. Due to the use of broad-spectrum antibiotics, most of these infections are very uncommon. Most infections originate from gram-positive skin flora and gram-negative organisms from bowel flora. Fungal infections such as candida or aspergillus can occur. The risk of fungal disease increases exponentially with the duration of neutropenia and the risk is also greatly increased in patients who are receiving steroids as treatment of graft versus host disease.
4. Interstitial Pneumonitis: This is usually a non-fungal and nonbacterial pneumonitis. There are multiple causes (table 7). There are numerous risk factors for this disease (table 8). The pathophysiology involves mononuclear cell infiltration and fluid accumulation in the pulmonary interstitium, with a relative sparing of the alveolar spaces. The clinical presentation involves hypoxemia with shortness of breath. A CXR usually reveals interstitial markings, which can be localized or diffuse. Fever may or may not be present. The most reliable way to make a diagnosis is by an open lung biopsy. The presentation of this disease is typical, but very frequently the etiology of this disease cannot be determined. Histologic examination of the tissue can reveal CMV inclusion bodies, inclusion bodies from other viruses, and Pneumocystis carinii. When autopsy fails to reveal any organism, the diagnosis of idiopathic interstitial pneumonitis is made.

TABLE 7

 Etiology of Interstitial pneumonitis

1. Infections
 Virus: CMV, HSV, VZV. Adenovirus, RSV and Measles virus
 Pneumocystis carinii
 Legionella
 Chlamydia trachomatis
 2. Irradiation
 3. Drugs
 Cytosan, Busulfan and Methotrexate
 4. Idiopathic
-

TABLE 8

 Risk factors for interstitial pneumonitis

Allogeneic transplant
 GVHD
 TBI: single dose, high exposure
 Prior radiotherapy to chest
 CMV seropositivity
 Transfusion with unfiltered CMV positive blood in a CMV seronegative patient
 Increasing age
 Methotrexate post transplant
 Female donor
 Omission of Septra prophylaxis

The treatment of interstitial pneumonitis depends on the etiology. In the past most were related to CMV infection, with a mortality upwards of 85-90%. Fortunately, with the use of either CMV negative or WBC depleted (filtered) blood products the exposure to CMV in seronegative donors can be virtually eliminated. In patients who are seropositive for CMV, weekly screening for CMV antigenemia allows for pre-emptive anti-viral therapy with agents such as Ganciclovir and Foscarnet. For patients with documented CMV disease the addition of high titer CMV IgG (Cytogam) is indicated.

Pneumocystis interstitial pneumonitis is treated with Septra, and recovery is seen in 80- 90% of patients. Rarely herpes simplex or varicella zoster can be the cause of interstitial pneumonia and most cases are successfully treated with acyclovir. Prophylaxis with either acyclovir or valcyclovir in HSV/VZV positive patients has been effective in decreasing the incidence of these infections. Mortality with idiopathic interstitial pneumonitis is about 50-60%, with some centers reporting success with the use of high dose steroids.

5. Acute Respiratory Failure: May occur due to overwhelming bacterial, fungal or viral sepsis. The prognosis is very poor for patients who require mechanical ventilation during BMT, particularly in patients who have not yet engrafted.

Late Complications

Restrictive pulmonary disease may occur as a late complication and is not correlated with any particular conditioning regimen or chronic GVHD. Generally this problem is mild and does not require specific therapy. Obstructive pulmonary disease, on the other hand, usually is secondary as a result of the chemoradiotherapy used in the preparative regimen or it can present as bronchiolitis obliterans, which is associated with chronic GVHD. Unfortunately the treatment options for bronchiolitis obliterans are few, infections should be treated promptly, and appropriate therapy for chronic GVHD if present should be instituted.

C. GASTROINTESTINAL COMPLICATIONS AND MANAGEMENT

Gastrointestinal complications are many. Several of these complications can be prevented by evaluation of liver and intestinal diseases prior to transplant.

In the post-transplant period the platelet count falls to very low levels, thus ulcerations in the intestinal tract that are bleeding or are likely to bleed should be healed prior to transplantation. Since granulocyte and lymphocyte counts fall in the post-transplant period, pre-existing fungal, bacterial and parasitic infections of the gut and liver should be identified and treated. Specific therapy is available for fungal, herpes simplex virus, cytomegalovirus and varicella zoster infections.

The presentation of infections in the immunosuppressed patients can be very subtle. Heartburn in a patient may be candida esophagitis; diarrhea may be giardia, cryptosporidia, or most commonly *C. Difficile* enteritis; eosinophilia may be strongyloides infection; elevated alkaline phosphatase may be due to fungal or mycobacterial infection.

Patients with pre-existing liver disease present several problems in the marrow transplant setting. Many have had multiple transfusions and come to transplantation with a previous exposure to hepatitis B or C. These patients are at a high risk of developing veno-occlusive disease after receiving chemoradiotherapy.

The liver and intestinal complications present with a similar sign/symptom complex.

NAUSEA/VOMITING/ ANOREXIA

In the first two weeks post-transplant, chemoradiotherapy toxicity and drug side effects are common causes. From the second week to the second month, acute GVHD, herpesvirus infections, and drug toxicity are more likely to occur.

1. Chemoradiotherapy toxicity: High-dose therapy causes more severe and prolonged symptoms than does normal dose chemotherapy. Oropharyngeal mucositis may last for several weeks, but nausea and diarrhea from chemoradiotherapy seldom persist beyond two weeks. Histologic healing parallels engraftment and is marked by improvement in symptoms.
2. Drug toxicity: The most common offenders are oral nonabsorbable antibiotics, amphotericin, cyclosporine, methotrexate, and Septra. The association between drug therapy and symptoms is usually obvious. Lipid infusions and high glucose or amino-acid levels in serum are also associated with nausea.
3. GVHD: Patients with GVHD involving skin, gut and liver are frequently nauseated and anorectic. Nausea and vomiting may also be seen in patients with less obvious GVHD.

4. Herpesvirus infections: Nausea and vomiting are prominent symptoms of CMV and HSV esophagitis. HSV is usually found in epithelial cells. Acyclovir is effective therapy for HSV and VZV infections. Ganciclovir is for CMV infections.
5. Other causes: Nausea and vomiting can be seen as presenting signs of peptic esophagitis, encephalitis, spontaneous subdural hematomas, septicemia, and adrenal insufficiency, as well as intra-abdominal processes such as cholecystitis, pancreatitis, and infiltrative liver disease. Some cases are never explained, but they usually improve over time.

GASTROINTESTINAL BLEEDING

Many marrow transplant patients will develop gross intestinal bleeding in the first 100 days. Many more will have occult bleeding, particularly when platelet counts are low. The most common sites for bleeding are the small intestine and esophagus, and the most common causes are GVHD, herpesvirus infection, peptic ulcer disease, and endoscopic biopsy sites.

1. GVHD: Many patients with gross bleeding suffer from GVHD. In addition, most of these patients have concomitant intestinal infection, typically viral mediated. These patients have extensive areas of mucosal ulceration, which fail to re-epithelialize due to ongoing immunologic injury. Platelet counts remain low in spite of transfusion. In the most severe cases, acute GVHD is refractory to treatment, platelets may become unsupportable, systemic infection supervenes and other organs fail and intestinal bleeding is a frequent terminal event.
2. Ulcers caused by infectious agents: CMV is the most common cause of isolated ulceration in the bleeding patient. Ganciclovir therapy and high-dose CMV titer IgG (Cytogam) is the gold standard in treating CMV enteric infections. Typically weekly surveillance assays for CVM antigenemia will become positive pre-dating active CMV infection, thereby allowing pre-emptive therapy. Other less common infections that can cause bleeding are fungal infections (candida, aspergillus), and a variety of organisms that cause epithelial necrosis in patients with GVHD. These include HSV, Adenovirus, Rotavirus, and Clostridium difficile. EBV-induced lymphoproliferative disease in the intestine can cause continuous bleeding from ulcerated nodules.
3. Peptic Ulcer Disease: When platelet counts drop below 30,000 per cu. mm., erosions and ulcers in the esophagus, stomach and duodenum may bleed steadily. These lesions tend to bleed early and have the best prognosis. Patients at risk routinely receive prophylactic therapy with Prilosec, Protonix, or Zantac.
4. Iatrogenic causes of Bleeding: Any biopsy of the GI tract can cause bleeding days to weeks after the procedure.
5. Mallory-Weiss tear: This is very uncommon. But it is common to find contused, hemorrhagic mucosa in the cardia of patients with persistent retching.

DIARRHEA

In the first few weeks, the preparative regimen and oral non-absorbable antibiotics are responsible. Later, acute GVHD and infections are causes of later cases. In patients with chronic GVHD the overgrowth of intestinal bacteria and fungi can cause intestinal malabsorption worsening the diarrhea that may already be present secondary to GVHD.

1. Chemoradiotherapy toxicity: Preparative regimens cause histologic changes in intestinal mucosa and secondary diarrhea. There is regeneration of normal epithelium by day 20 in almost all patients, with resolution of diarrhea.
2. Medications: Oral nonabsorbable antibiotics cause mild diarrhea in the fasting state and more when food is ingested. Patients receiving oral or parenteral antibiotics may have diarrhea with or without over growth of *C. difficile*. Other diarrhea causing drugs in this setting include magnesium salts, metoclopramide and methotrexate.
3. Acute GVHD: Voluminous diarrhea is a prominent manifestation. The onset of acute GVHD is usually between day 20 and 60. Patients receiving mismatched transplants, or those who can not tolerate immunosuppressive therapy may develop hyperacute GVHD, with onset as early as one week. The diarrheal fluid is high in protein content. Associated symptoms include anorexia, nausea, vomiting, and crampy abdominal pain, which is partially, relieved by passing diarrheal stools. Food intake worsens the symptoms. The diagnosis is made on clinical grounds but may be confirmed by mucosal biopsy.
4. Intestinal Infections: Viral, fungal, parasitic, and bacterial infections can produce diarrheal illness that is similar to GVHD, but they more commonly coexist with or complicate acute GVHD. One reason for this is the immunosuppressive drugs used to treat GVHD, as well as the immune abnormalities caused by GVHD itself. In the first few weeks after transplantation, enteric infections present at the time of conditioning therapy may worsen, coincident with ablation of the patient's marrow. Examples are *Giardia* and fungal enteritis. Enteric pathogens such as *Salmonella*, *Shigella* and *Campylobacter* are rare in the protected environment of the BMT unit. *C. difficile* toxin diarrhea is a frequent pathogen seen. Diarrhea that occurs later may be secondary to viral pathogens. Common viruses are CMV, rotavirus, adenovirus, HSV, and Coxsackievirus. The diagnosis is made by viral cultures from either endoscopy or stool culture.
5. Chronic GVHD: Diarrhea is uncommon after 100 days, but maybe chronic GVHD. In this disease, there is an associated immunodeficiency syndrome, including deficient secretory IgA production. If chronic GVHD is not diagnosed early, it may be complicated by superinfection with bacterial and fungal overgrowth.

ESOPHAGEAL COMPLAINTS

In the early post transplant period, oropharyngeal mucositis, fungal or bacterial esophagitis, and intramural hematoma of the esophagus are causes of dysphagia, heartburn, and painful swallowing. From day 30 to 75, herpesvirus and reflux esophagitis are common. After day 100, chronic GVHD involving the esophagus is the most common cause of dysphagia.

1. Mucositis: Painful desquamation of epithelium in the mouth, pharynx, and upper esophagus is a common toxic effect of chemoradiotherapy and methotrexate. HSV may also produce these symptoms. Patients frequently cannot initiate swallowing because of pain. Analgesic therapy with a morphine drip \pm patient controlled anesthesia may be used.
2. Infectious esophagitis: CMV, HSV and fungal esophagitis were once equally common causes of esophagitis. HSV and fungal esophagitis have become less frequent because of

prophylactic therapy with acyclovir and antifungal drugs. CMV is less common because of the use of CMV-screened or leukodepleted blood products and surveillance CMV antigenemia screening. Fungal infections of the esophagus occur at two stages after marrow transplantation during the early granulocytopenic stage, and during the long recovery of T - cell function. *Candida albicans* is the most common fungus isolated, but other candida species and other fungi can be found. The treatment of choice is intravenous amphotericin B. Bacterial esophagitis usually occurs as part of a mixed infection. The organisms, derived from oral flora, may cause septicemia. Viral esophagitis usually appears after day 40, and is more common in patients receiving immunosuppressive treatment for GVHD. Late sequelae of HSV esophagitis include stricture formation.

3. Acid-Peptic Esophagitis: Once infection is ruled out, esophagitis is attributed to acid-peptic disease. Factors contributing to reflux include gastric stasis, esophageal dysmotility caused by inflammation and poor salivary flow related to mucositis and GVHD. Because of the marrow suppressive effects of H2-antagonists, sucralfate and antacids are
4. Chronic GVHD: Some patients with chronic GVHD have esophageal involvement, presenting with dysphagia, retrosternal pain, insidious weight loss, and aspiration. Barium contrast x-rays may reveal webs, rings, and tight strictures in the upper and mid-esophagus. Patients with this problem clear acid from their esophagus poorly, and may develop distal esophagitis. Treatment with dilations, antireflux measures, and immunosuppressive therapy is successful if started early,
5. Intramural hematoma: Acute onset of retrosternal pain and hematemesis in patients with low platelet counts suggests intramural hematoma. This usually occurs after vomiting or retching but can occur spontaneously. The diagnosis is best made with water-soluble contrast and CT. Endoscopy can be done, but noninvasive imaging is safer. Pain and dysphagia resolve spontaneously usually after two weeks.

ABDOMINAL PAIN

In the first weeks after transplantation, the most common causes of pain are hepatic enlargement from VOD and intestinal toxicity from chemoradiotherapy. Later, acute GVHD and infectious enteritis are common causes of pain. Patients can also experience pain as a result of more unusual causes as well such as hematomas, typhlitis, herpes zoster, and liver abscess.

1. Veno-occlusive disease (VOD): About 75% of patients with VOD have pain from hepatic enlargement, with onset from day 5 to 15. The intensity ranges from mild right upper abdominal tenderness to severe, generalized abdominal pain; in some patients this is the first manifestation of VOD. Clues to the diagnosis of VOD include weight gain in the preceding days, enlarging liver, and jaundice. The treatment of VOD is primarily supportive (maintaining euvolemia with good urine output through diuretics) with all but the severe cases resolving spontaneously.
2. Intestinal Toxicity from Chemoradiotherapy: Many patients develop diarrhea and crampy abdominal pain after their preparative regimen, but this is self-limited. Rarely does tile

preparative therapy cause mucosal necrosis, severe abdominal pain, ileus, or peritoneal tenderness.

3. Acute GVHD: Crampy midabdominal pain, partially relieved by passing diarrheal stools, is a common presentation of acute GVHD, along with skin rash and jaundice. When pain becomes severe and unrelenting one should become concerned about perforation, *C. difficile* colitis, or superinfection with fungi and viruses.
4. Medications: Early in the post-transplant period, continuous narcotic administration (usually for painful mucositis,) can lead to ileus, distention, and pain. Antiemetic drugs with anticholinergic properties worsen the problem. Attempts to treat the pain with opiates and anticholinergic drugs can lead to massive, painful distention.
5. Infection: The range of organisms that can cause infection has been discussed previously. Fungal, and rarely bacterial, abscesses extensive enough to cause severe pain are usually visible by CT and ultrasound. Smaller lesions in the liver can cause discomfort and escape detection. Viral infections can cause pain in different ways. Visceral infection with VZV may present as abdominal pain, ileus, and fulminant hepatitis. CMV may also infect neural plexi within the intestine, causing pseudoobstruction and distention. CMV, and other viruses, may also cause acute pancreatitis.
6. Typhlitis: Its presentation may be confused with acute GVHD. The sudden onset of right-sided abdominal pain, vomiting, fever, and diarrhea should be a clue. This rapidly progresses to septicemia and shock. Mortality is high in patients with poor marrow function. *Clostridium septicum* is the most frequently isolated organism, Imaging studies showing massive cecal wall edema and a rapidly deteriorating clinical course suggest typhlitis. Differentiating typhlitis from acute GVHD may be impossible short of laparotomy. This is fortunately an uncommon problem.
7. Hematomas: Patients with low platelet counts may bleed into the retroperitoneum, the abdominal wall, and the intra-abdominal viscera. The pain of retroperitoneal bleeding is usually abrupt and located in the lumbar region. Intramural bleeding is common in the esophagus, usually after retching, or after biopsy. Sudden retrosternal pain and signs of esophageal obstruction are the presenting features,
8. EBV-Induced Lymphoproliferative Disorder: Rarely, infiltration of the viscera with transformed B-Lymphocytes may cause severe abdominal pain, hepatosplenomegaly, ileus, and intestinal bleeding. It occurs in post-transplant patients with who are receiving immunosuppressive drugs. The intestinal wall becomes infiltrated with a lymphoma-like proliferation of cells. In addition, large ulcerated nodules can be found in the stomach and small intestine. Although EBV is the apparent trigger to this proliferation of B-Lymphocytes, treatment with antiviral agents has not been effective. Stopping the immunosuppressants may reverse the process but not uncommonly anti-neoplastic therapy is indicated.
9. Biliary pain: Gallbladder sludge is a common finding in patients on TPN. Acalculous cholecystitis occurs uncommonly, but can mimic a surgical abdomen. Some patients, who resume eating after a stormy post transplant course, may develop acute biliary colic from passage of sludge into the common bile duct.

LIVER DISEASE

The common diseases VOD and GVHD are relatively easy to tell apart, but when GVHD occurs early diagnostic confusion is possible. In the first few weeks after transplant chemoradiotherapy commonly causes liver damage (VOD), whereas acute GVHD typically occurs later after engraftment (after day +20). Throughout the post transplant period, drug-liver injury (including TPN toxicity) and the effects of sepsis, endotoxemia and hypotension are always diagnostic considerations. After day 100, chronic viral hepatitis, chronic GVHD, and drug-liver injury occur.

1. **Veno-occlusive disease (VOD):** This is characterized by hepatomegaly, jaundice, weight gain, and is marked histologically by occlusion of terminal hepatic venules, and damaged hepatocytes. The risk factors are transplant for many ages, previous history of hepatitis, and a second transplant. It is more rare in patients with aplastic anemia, thalassemia, and illnesses that do not require high-dose conditioning therapy. It is also less frequent among autologous marrow recipients. The diagnosis is made on clinical grounds. Patients gain weight and become jaundiced. Most develop right upper quadrant pain, liver tenderness, and may accumulate ascitic fluid. The serum bilirubin (primarily the direct fraction) usually rises early and peaks within two weeks. There are only a few other causes of significant liver disease before day 20, the most common is "hyperacute" GVHD. The clinical diagnosis can be accurate, thus biopsy is not usually necessary. Management of severe VOD is unsatisfactory, since there is no treatment for venule occlusion or hepatocyte necrosis. The patient's intravascular volume and renal perfusion are maintained with blood, colloid and albumin infusions, while avoiding intra and extravascular fluid accumulation. Kidneys are at a risk from volume depletion and nephrotoxic drugs. Encephalopathy can occur. Diagnostic difficulties arise when VOD blends into GVHD.
2. **Acute GVHD:** Liver abnormalities include cholestasis, mild hepatocellular necrosis, usually in patients with skin and intestinal GVHD. There are moderate to marked increases in serum bilirubin and alkaline phosphatase, and to lesser extent hepatocellular enzymes. A clinical diagnosis of liver GVHD can be made when it develops during days 20-40 in a patient with no signs of VOD, sepsis, shock, viral infection, drug-liver injury, or biliary obstruction. Acute skin GVHD can be confirmed by skin biopsy. If the diagnosis is uncertain due to lack of skin involvement, a liver biopsy may be helpful. For the treatment of acute GVHD, prednisone and anti-thymocyte globulin (ATG) are the most commonly used front-line therapy. The response to treatment depends on the severity of the disease.
3. **Infections:** Fungal and bacterial infections of the liver are usually seen during granulocytopenia and immunosuppressive drug therapy for GVHD. Fungal infection presents with fever, tender hepatomegaly, and elevated serum alkaline phosphatase. Diagnosis depends on CT and directed fine needle aspiration. Empiric amphotericin B therapy is used. Bacterial abscesses and cholangitis are uncommon, probably because of the use of broad-spectrum antibiotics. Mycobacterial organisms may be reactivated during prolonged immunosuppression after transplant. Liver dysfunction may be seen with remote bacterial infections, especially with gram negative and pneumococcal infections. Viral infections of the liver are not common early after transplantation but hepatitis B or C may reactivate later. Other viral causes of fulminant hepatitis are HSV and VZV, which are potentially treatable with Acyclovir. CMV infection of the liver is a common finding in patients with disseminated CMV infection. Treatment includes with Ganciclovir or Foscarnet.

4. Drug induced Liver injury: TPN causes usually asymptomatic mild elevations of serum liver enzymes. Cyclosporine and FK506 are the most hepatotoxic of the immunosuppressive drugs, and can cause cholestasis and even hepatocyte necrosis. It may also potentiate chemoradiation hepatotoxicity. Methotrexate is also hepatotoxic. ATG may cause mild elevation of liver enzymes. Azathioprine, rarely used in chronic GVHD, may cause cholestatic and hepatocellular damage. Most antimicrobial drugs used are not hepatotoxic. Sulfa containing drugs used for prophylaxis may cause cholestasis, hepatitis and liver failure. Ketoconazole may also cause potentially fatal hepatitis and is rarely used in the BMT setting.
5. Chronic GVHD: Most patients will have had acute GVHD earlier. Liver involvement occurs in 90% of patients. Elevation of bilirubin, alkaline phosphatase and hepatocellular enzymes are found. The differential diagnosis includes viral hepatitis and drug-liver injury. Biopsy can be diagnostic. Current drugs used in the treatment include prednisone, cyclosporine or FK506, Cellcept (Mycophenolate), and others.

D. INFECTIONS COMPLICATIONS AND MANAGEMENT

Bone marrow transplant patients remain severely immunosuppressed some months after transplantation. Immunologic recovery is gradual and variable, and certain processes (e.g. GVHD) and therapies (e.g. corticosteroids) are additionally immunosuppressive. This is the reason why infections are a major cause of morbidity and mortality. The most immediate change in host defenses, is the precipitous loss of circulating granulocytes, which occurs at the time of disruption of many anatomic barriers, such as the oral and gastrointestinal mucosa. By day +20-30 days the granulocyte count usually has recovered to above 1000 per cu. mm., however, their function is not completely normal. The recovery of lymphocyte mediated immunity is also delayed. Total lymphocyte counts become normal by the second month after transplant, but the proportion and sometimes the absolute number of T cells may be abnormal for prolonged periods. The number of helper-inducer cells remains low, while the number of cytotoxic-suppressor cells returns rapidly to normal. Some lymphocyte functions in vitro, including reactivity in mixed leukocyte culture and in response to mitogens or viral antigens are depressed for months. By contrast, cytotoxic activity appears soon after transplant.

Serum immunoglobulin levels are low or low normal for up to 1-year post BMT. As a result some patients require IV IgG biweekly until at least day 100.

Many of these immunologic functions are more depressed in patients with GVHD. These patients are at risk of additional infections for longer periods than patients without GVHD.

The post transplant course may be divided into three periods that correspond broadly to the pattern of immunologic recovery. First, the early granulocytopenic period lasts 20-30 days after transplant in most patients and may be highlighted by fever and bacterial or fungal infection. Second, between recovery of circulating granulocytes and day 100, viral and protozoan infections may be more frequent. A diffuse, interstitial pneumonia may occur during this interval. Bacterial infections continue to occur, and fungal infections overlap both early phases, especially in the small number of patients with prolonged granulocytopenia because of graft rejection or graft failure. Third, after day 100 the incidence of most infections decreases. Characteristic infections that do occur include VZV infection and bacteremic pneumococcal infection. The risk of infection increases with the occurrence of GVHD due to depressed marrow function and immune suppression secondary to treatment. It must be emphasized that not all patients behave so predictably. One must entertain new possibilities and use aggressive diagnostic and therapeutic techniques in the care of these patients.

PRE- TRANSPLANT PHASE (BEFORE DAY 0)

The immune status of patients prior to transplant is heterogeneous. Factors that predispose to infection after transplantation should be evaluated before transplantation. These include: a history of previous infection that might be reactivated through immunosuppression, organ obstruction, indwelling intravenous devices and status of infectious diseases in the marrow donor. Most of the infections during this phase are temporally related to falling granulocyte count.

POST -TRANSPLANT PHASE (DAY 0 TO 30)

This is the period of profound neutropenia, and the problems arising are generally bacterial and fungal infections. The mucosal disruption produced by the preparative regimen predisposes to infection. The placement of indwelling central venous catheters predisposes to infections with gram-positive organisms. The clinical diagnosis of infection is complicated by the absence of many of its classical signs. Despite severe infection, localized sites may show minimal signs. For example, perirectal infection may be marked by pain only and not by swelling or erythema. Because of profound neutropenia the typical signs of infection are minimized, and an inadequately treated infection in a bone marrow transplant patient can be lethal. All febrile, neutropenic patients should be given immediate empiric broad-spectrum antimicrobial therapy. Our center uses monotherapy with Cefepime in the uncomplicated neutropenic fever setting.

For patients who respond to empiric antibiotic coverage, therapy is usually continued until the absolute neutrophil count exceeds 500 per cu. mm. Patients with moderate or severe acute GVHD should be continued on antibiotics. For patients who remain febrile after 3-7 days of antimicrobial therapy, a second antibiotic \pm Amphotericin B is added since deep fungal infections are common and very difficult to diagnose antemortem. Other causes of persistent fever must also be considered, including resistant bacterial infection, drug fever, and indwelling central venous line infection.

Patients experience severe therapy-related mucositis. This predisposes the patient to bacterial infection, and reactivation of oral (or genital) herpes simplex infections. These lesions can be confused with therapy-induced mucositis. Systemic acyclovir prophylaxis is very effective. Topical antifungal agents such as clotrimazole may be useful in preventing oropharyngeal candidiasis.

INTERMEDIATE POST-TRANSPLANT PHASE (DAYS 30-100)

After neutrophil recovery, bacterial and fungal infections usually become less frequent, however, severe humoral and cellular immunosuppression persists beyond this period. In addition GVHD may present during this phase, requiring increased immunosuppressive therapy. The most important infections occurring in the interval between successful engraftment and day 100 are viral or protozoan. Nonbacterial and non-fungal or interstitial pneumonitis is the most notorious and overwhelming of these. Interstitial pneumonitis is caused by CMV, pneumocystis carinii (PCP), adenovirus, herpes simplex virus, Legionella pneumophila, but is most commonly idiopathic.

Effective prophylaxis can be achieved against PCP with Septra. However, due to its myelosuppressive potential, it should be started after neutrophil counts recover. Septra is used 2-3 days a week and is continued for 6 months after all immunosuppressive medications are

discontinued. There incidence of interstitial pneumonitis due to CMV is greatly decreased by the use of CMV-negative or leukodepleted blood products in CMV seronegative donor and patient. Following weekly assays for CMV antigenemia allows for pre-emptive therapy with Ganciclovir or Foscarnet prior to the onset of CMV disease.

Management of patients with interstitial pneumonitis should be aggressive. Bronchoalveolar lavage should be performed and if non-diagnostic, and open lung biopsy should be considered.

LATE POST-TRANSPLANT PHASE (DAY >100)

Infections occurring after 100 days are determined in part by the residual immune deficiency shared by all patients and in part by the additional immunosuppression associated with GVHD and its treatment.

Many bone marrow transplant patients develop VZV infection. In some patients it is a true primary infection, whereas in others it is probably an atypical generalized zoster. One-third of patients with untreated herpes zoster can develop cutaneous dissemination. The case-fatality rate for untreated varicella is 35%, and for untreated herpes zoster with dissemination is 30%. Other syndromes that present with zoster infection are trigeminal zoster with keratitis, post-herpetic neuralgia and local scarring or bacterial superinfection. The incidence of VZV infection is increased among patients with allogeneic transplants and among those with acute or chronic GVHD. Because of the high mortality of patients with VZV infection, those patients who are VZV or HSV positive are given acyclovir or valacyclovir prophylaxis.

In patient with chronic GVHD, common late infections are upper respiratory or pulmonary infections. *Streptococcus pneumoniae* is a common isolate, followed by *Staph aureus*. The presumed explanation for bacteremic pneumococcal infections is that patients do not make opsonizing antibody to encapsulated organisms. Patients respond poorly to immunization with pneumococcal vaccines for the first 1-2 years after transplant. Septra prophylaxis is continued in patients with chronic GVHD to prevent PCP pneumonia.

E. HEMATOLOGIC COMPLICATIONS AND MANAGEMENT

Engraftment of donor hematopoietic cells is detected by a rising peripheral blood granulocyte count usually within 2 to 4 weeks after BMT. Reconstitution of erythrocyte and platelet lineages typically follows during the next 2 to 8 weeks. After conditioning and before reconstitution, BMT patients require multiple transfusions of packed red blood cells and platelets. It is absolutely essential that only irradiated blood products be administered because even small numbers of mismatched allogeneic cells may potentially engraft the patient and produce fatal GVHD. The use of only CMV-negative or unscreened but leukodepleted blood products decreases the risk of CMV infection.

An important question raised frequently after BMT is whether the cells repopulating the peripheral blood and marrow represent true engraftment or autologous recovery. This is an especially important issue in children undergoing BMT for immunodeficiency disorders, who receive minimal conditioning chemotherapy. Presence of cells of donor origin is most easily assessed when the donor and recipient are of different sexes. Analysis of ABO and minor blood group antigens is sometimes helpful, although the fact that most BMT patients are multiply transfused often confounds the issue. In patients receiving haploidentical transplants, HLA typing of marrow cells can identify whether a subpopulation bearing unique donor antigens is

present. For most patients the best and most quantitative assay for engraftment is the use of DNA analysis such as STR assays.

Red Cell Transfusion

Since the mean life span of erythrocytes is approximately 120 days, anemia is less of a problem than neutropenia and thrombocytopenia. However, because of bleeding complications from thrombocytopenia and daily blood drawing for tests which adds up to a significant volume, many red blood cell transfusions are required.

Generally, it is good transfusion policy to keep the patient's hematocrit above 20%. To minimize the circulatory overload transfusions given are packed red blood cells. The blood given must be irradiated to avoid GVHD caused by lymphocytes present in the packed cells.

Platelet transfusion

Peripheral platelet counts of 15-20,000 per cu. mm. have become widely accepted as an indication for prophylactic platelet transfusions. Undoubtedly in the setting of bleeding, platelets should be administered if they are below normal levels. Special circumstances may require raising the threshold for prophylactic transfusion of platelets, e.g. prevention of CNS bleeding or active bleeding elsewhere.

In patients with splenomegaly or pyrexia, the rate of consumption of platelets may be substantially increased.

In some cases thrombocytopenia is caused by reasons other than slow marrow engraftment. These include: disseminated intravascular coagulation; drugs that inhibit platelet function, such as aspirin and NSAID's; and splenomegaly. The metabolic status of the patient including hepatic and renal failure may inhibit platelet function and put patients at risk of bleeding even in non-thrombocytopenic conditions.

Several factors can affect the efficacy of platelet transfusions, they include fever, septicemia, DIC, an enlarged liver or spleen, alloimmunization, and the duration of platelet storage.

Neutropenia

The use of G-CSF may be used to decrease the duration of neutropenia in transplant patients or to increase the number of neutrophils for patients whose counts are suppressed by medications such as Ganciclovir or by GVHD.

F. NEUROLOGIC COMPLICATIONS AND MANAGEMENT

The nervous system is exposed to many sources of neurologic injury during the course of BMT (Table 9). They originate from the side effects of chemotherapy and/or irradiation given in the pretransplant period, from infections occurring in the post-transplant immunodeficient period, or as a result of therapies administered to control GVHD. System failure in other organs also commonly produces central nervous system dysfunction.

TABLE 9

Neurologic complications

CNS infections

Vascular

Encephalopathy

Secondary malignancies and neoplastic recurrence

Cerebellar and spinal cord syndromes

Peripheral nerve disorders

Drug induced neurotoxicity

CNS INFECTIONS

1. Fungus

Aspergillus: The most frequent CNS infections are fungal. CNS involvement in the form of a brain abscess is relatively common in patients who have disseminated aspergillosis. *Aspergillus* is primarily a respiratory pathogen, thus the majority of infections involve the sinus or the lungs. Since *aspergillus* tends to invade the blood vessels, the infection disseminates throughout the body. The infection can progress through the soft tissues, cartilage, and bone. It can progress through base of the skull to involve the brain. Amphotericin B is the initial treatment of choice. Newer agents useful in treating *aspergillus* include Caspofungin and Voriconazole.

2. Candida: Hematogenous dissemination may manifest with retinal abscesses (symptoms: orbital pain, blurred vision, scotoma, opacities). Meningitis and brain abscesses occur in patients with disseminated infection. Diagnosis may be difficult since the fungus may not be successfully cultured. The treatment of choice is Amphotericin B.

3. Cryptococcosis: Usually acquired prior to hospitalization. Infection begins in the lung, but the patient may remain asymptomatic. Dissemination of the infection may occur after BMT. It may manifest as meningoencephalitis. Early manifestations are headache, nausea, staggering gait, irritability, confusion, and blurred vision. Fever and nuchal rigidity are usually mild or absent. CXR may disclose a dense infiltrate if infection is present. Lumbar puncture is a useful test. The definitive positive test is growth of a culture.

Bacteria

Meningitis due to bacteria is rare, but it may occur late in patients with chronic GVHD. *Pneumococcus*, *meningococcus*, *hemophilus influenzae*, and *klebsiella pneumoniae* are the most common pathogens. The manifestations are those of bacterial meningitis. Occasionally brain abscesses from *staphylococcus aureus* are seen.

Viruses

Viral infections are infrequent and prophylactic acyclovir makes them even more uncommon. Patients who are not receiving prophylaxis with acyclovir, or those with chronic GVHD are at risk for HSV or disseminated VZV. Early diagnosis of HSV can be obtained by

MRI and EEG. The definitive diagnosis is HSV isolation by biopsy. Treatment with acyclovir is effective when started early.

Toxoplasmosis

Reactivation of quiescent infections can occur. Most infected patients have signs and symptoms of encephalitis and almost all have brain involvement on autopsy if they do not survive. Neurologic signs are variable. Toxoplasma can be isolated from the peripheral buffy coat cells and inoculated human fibroblasts. Treatment consists of pyrimethamine and sulfadiazine.

VASCULAR COMPLICATIONS

Cerebrovascular complications are relatively uncommon. They include subarachnoid hemorrhages, parenchymal infarcts and hemorrhages. Most infarcts in BMT recipients appear to be related to cardiac emboli.

ENCEPHALOPATHY

The single most common neurologic complication seen in BMT patients is probably metabolic encephalopathy. In order of decreasing frequency, the causes include hypoxia and/or ischemia, hepatic failure, electrolyte imbalance, and renal failure. An uncommon complication with severe, often fatal, neurologic sequelae is the development of leukoencephalopathy. Leukoencephalopathy is a complication of therapy in the treatment of CNS leukemia and lymphoma. It usually occurs when intrathecal MTX, high-dose MTX, and cranial irradiation are all administered pre-transplantation. There have been documented cases from one to 14 months after transplant.

SECONDARY MALIGNANCIES AND NEOPLASTIC RECURRENCE

Leukemic recurrence in the CNS after BMT is more common for ALL than ANLL. A variety of secondary malignancies have been reported.

CEREBELLAR AND SPINAL CORD SYNDROMES

This complication has been infrequently reported. They are related to the effects of various cytotoxic chemotherapies and immunosuppressive agents. Cerebellar syndromes have also been described in BMT patients in association with cyclosporine and FK506. Symptoms noted include ataxia, confusion, somnolence, mild weakness, seizures, and loss of deep tendon reflexes and extensor plantar responses. Most symptoms clear with discontinuation or reduction of cyclosporine or FK-506. Diseases of the spinal cord are rare. Causes include chemotherapeutic toxicities, infections, and possible vascular or paraneoplastic necrosis.

PERIPHERAL NERVE DISORDERS

Except for dermatomal herpes zoster infections or peripheral neuropathies from chemotherapy, peripheral nerve disorders related to BMT are uncommon. Polyneuropathy has been described with cyclosporine. Patients with pre-existing leukemias who have received chemotherapy may also have peripheral neuropathies.

DRUG INDUCED NEUROTOXICITY

Cytosine Arabinoside (ARA-C)

Toxicity is related to the dose administered and not duration of exposure. Symptoms usually develop within 6-8 days after the first dose and may include personality changes,

disturbances in the level of consciousness, headache, somnolence, confusion, scotoma, paraplegia, cerebellar toxicity, and occasionally seizures.

Cyclosporine

Patients may present with tremor, mental confusion, muscle weakness, paraesthesia, seizures, transverse myelitis, quadriparesis, cerebellar ataxia and drowsiness. Some of the neurologic symptoms have been linked to a low level of serum magnesium.

Acyclovir

Less than one percent of patients receiving intravenous acyclovir can develop encephalopathic changes characterized by lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma.

Steroids

Neurologic complications can manifest as headache, psychosis, vertigo, convulsions and increased intracranial pressure.

G. RENAL COMPLICATIONS AND MANAGEMENT

In contrast to the liver, the kidneys are rarely the primary target of a pathological event after BMT. GVHD does not visibly affect the kidney, and no specific disease entity related to radio-chemotherapy has been observed. It is likely that subclinical degree of tubular damage occurs during the preparative regimen. Renal impairment is predominantly secondary to circulatory disturbances associated with veno-occlusive disease, septicemia, or hypovolemic shock. Furthermore, some of the drugs frequently used post-transplant can injure the tubular system. The severity of renal impairment can range from mild prerenal insufficiency to acute oliguric renal failure.

Renal insufficiency secondary to circulatory problems

This occurs as a consequence of intravascular volume depletion, and associated hypotension. Common causes are capillary leak syndrome, severe gastrointestinal losses and septic shock. Severe prerenal insufficiency may lead to acute oliguric renal failure. Treatment should be directed at maintaining sufficient intravascular volume by infusion of fluids and dose reduction of possible nephrotoxic drugs such as cyclosporine, FK506, amphotericin B and aminoglycoside antibiotics.

In severe cases of prerenal insufficiency or toxic damage, acute renal failure secondary to acute tubular necrosis can develop, in particular when nephrotoxic drugs are given at the same time. Common causes include prolonged hypotension, and the hepatorenal syndrome from severe veno-occlusive disease. Some patients may require dialysis. It is advisable to keep the hemoglobin above 10 grams/dl to provide sufficient oxygen to the kidney. Low dose dopamine (3-5 mcg/kg/min) may be beneficial. The prognosis of renal impairment secondary to prerenal insufficiency is usually good.

DRUG INDUCED RENAL TOXICITY

Numerous potentially nephrotoxic drugs are used in the transplant setting. They include cyclosporine and FK506, various antibiotics, antifungal and antiviral agents.

Aminoglycosides

Usually used for prophylaxis of infections with gram negative bacteria. They are nephrotoxic in a dose-related fashion. They may lead to mostly reversible focal necrosis and interstitial proliferation. The degree of nephrotoxicity seems to vary between different aminoglycosides.

Cyclosporine/FK506

Nephrotoxicity of cyclosporine is associated with renal vascular injury, likely due to inhibition of prostacyclin. Early signs of damage consist of proteinuria, bicarbonate loss, impaired urinary concentrating ability and urinary casts.

Some renal function impairment can be expected in every patient. Volume depletion, additional nephrotoxic drugs, hepatic dysfunction, septicemia, and prolonged hypotension are associated with a more rapid rise in creatinine. Renal dysfunction is usually reversible after withdrawal of cyclosporine/FK506, even in patients who have had elevated serum creatinine levels for several months. However, if severe renal damage has occurred, recovery might not be complete and chronic renal damage may persist. In some patients, a syndrome reminiscent of the hemolytic-uremic syndrome with renal insufficiency has been reported.

If renal dysfunction develops in patients on cyclosporine or FK506 therapy, some drug adjustments are recommended. If creatinine rises markedly, 1-2 doses should be withheld, hydration should be increased and other nephrotoxins should be discontinued. When creatinine rises gradually, the dosage should be reduced by at least 25%. In the pediatric patient, if the creatinine is between 1.5 to 2.0 mg/dl, the daily dose should be reduced by 50%. And, if the creatinine exceeds 2.0 mg/dl, cyclosporine should be held.

Acyclovir

Renal damage can occur with high intravenous doses. Crystal formation in the renal tubules has been described. Slow infusion with adequate hydration prevents many complications. If renal failure develops, and creatinine clearance is below 50 ml/min an acyclovir dose reduction is required.

Drug Induced Hemorrhagic Cystitis

Hemorrhagic cystitis is the most frequent serious side effect of high dose cyclophosphamide. It is caused by the urotoxic metabolite acrolein. The incidence of this complication can be reduced by forced diuresis with or without bladder irrigation. Nonetheless, about 30% will develop cystitis despite these protective measures. A more common approach is the use of Mesna. When administered intravenously, it is rapidly excreted via the urinary tract. Within the urinary tract, it combines with acrolein to form a non-toxic compound.

Etoposide at high doses can also cause hemorrhagic cystitis, however it can be prevented by forced diuresis.

Treatment options for hemorrhagic cystitis are limited. Vigorous continuous hydration should be given. Intravesicular prostaglandin E has been reported to be successful in some patients. Some patients may require cauterization of bleeding mucosa via cystoscopy.

The course of hemorrhagic cystitis can vary greatly. Some patients experience a short period of hematuria following chemotherapy administration. In others, it occurs with some time lag and may manifest itself, for example, when the patient develops severe thrombocytopenia. An occasional patient may develop bladder spasms and may be plagued by reduced bladder capacity.

INFECTIONS

Infectious complications of the kidney are not very frequent. Bacterial renal infections such as pyelonephritis are rarely encountered. Kidney involvement often occurs as part of a systemic infection, and renal impairment can develop as a consequence of bacteremia and shock. On autopsy, about 7% of BMT patients show involvement of the kidney with fungus, with *Candida* most commonly.

Viral infections can occur. Systemic CMV infection can affect the kidney. Hemorrhagic cystitis that develops late may be of viral etiology, particularly BK virus or adenovirus. In a series of 1,000 patients, adenovirus was isolated from the urine in 10% of patients. One quarter of patients had decreased renal function. About the same number of patients presented with cystitis, but only half of those had positive cultures for adenovirus. Most patients with adenovirus infection also have signs of disseminated disease involving organs such as lung, gut and liver. Histologic changes seen in adenoviral infection are viral inclusions associated with tubular epithelial necrosis. Isolation of patients does not seem to prevent infections with adenovirus, suggesting an endogenous source.

Besides adenovirus, polyomaviruses such as BK virus, have been associated with late onset hemorrhagic cystitis. There is no treatment for adenovirus and polyomavirus infections. If the patient has GVHD and is being treated with immunosuppressive drugs, a dose reduction may be considered. Intravenous immunoglobulin has been used but no data is available on its efficacy.

H. ENGRAFTMENT FAILURE

To achieve sustained marrow engraftment the donor marrow must contain enough viable pluripotent stem cells. Immunosuppressive therapy must be given to the recipient in order to blunt the host versus graft response, and allow the donor-derived cells to replace the patient's lymphohematopoietic system. Several tests can be used to document donor cell engraftment, e.g. cytogenetic analysis, erythrocyte typing, HLA typing, and RFLP or STR analyses. In some instances transplant recipients can become "mixed chimeras" for prolonged periods of time, meaning they have both host and donor cells.

The mechanisms for engraftment failure are not well understood. There are four situations in which the reasons for engraftment failure are thought to be understood:

1. Pre-sensitized patient: Sensitization of the recipient to minor histocompatibility antigens presumably shared between transfusion donors and marrow donors and not expressed on recipient cells. Exposure to those same antigens at the time of transplantation, therefore, represents a secondary immune response more difficult to suppress with conventional methods than a primary immune response encountered in nonsensitized patients.

Pretransplant transfusions in patients with lymphohematopoietic malignancies are apparently not associated with an increased risk of marrow graft rejection. Presumably this is due to the more aggressive cytotoxic therapy used.

2. Histo incompatible transplants: Failure of engraftment has generally not been a problem with HLA identical marrow grafts, except in certain patients with severe aplastic anemia, and sickle cell disease. However, with histo incompatible grafts, dependent upon the degree of mismatch, as many as 15% of patients have shown failure of sustained engraftment, or incomplete hemopoietic reconstitution by donor cells. Approaches to histo incompatible grafts have included increased doses of TBI, the addition of chemotherapy, or the use of ATG.

4. T -Cell Depletion: T -cell depletion reduces the incidence of acute GVHD, but chronic GVHD still occurs. However, along with this very encouraging finding of reduced or absent acute GVHD, several rather disturbing observations have been made. The first is the failure of sustained engraftment. T lymphocytes removed from the marrow graft may have an immunosuppressive effect that is lost. Alternatively, T lymphocytes may have an amplifier effect on transplanted hemopoietic stem cells, thus generating a growth advantage and leading to "take over" the host. In addition T-cell depletion is associated with an increased relapse rate post-transplant secondary to a reduction in the graft versus leukemia effect.

I. PSYCHOSOCIAL COMPLICATIONS AND MANAGEMENT

There are several stages that children and families go through in the transplantation procedure. The first stage starts with the decision to accept treatment, the initial admission, evaluation and care planning. This stage is followed by entry into relative isolation, followed by the transplant, waiting for graft acceptance or rejection and for possible complications, and finally preparation for discharge and adaptation to life outside the hospital. Before transplantation, children often describe fears of life-threatening disease, along with anxiety about illness and death, feelings of being a burden to the family, low self-esteem, helplessness and vulnerability. During transplantation the major problems are those of anxiety, depression, overdependency and regression, along with anger, reduced tolerance for procedures and periodic refusal to cooperate. As they become more gravely ill, they often request that they not be left alone. Some also deny symptoms or become apathetic and helpless as the procedure continues, while others alternate between hope and fear in the post-transplant period.

Children suffering from the stresses of a bone marrow transplant procedure have fewer and less severe frank psychiatric disorders than might be expected. Adjustment disorders with depressed mood, organic mental disorders, and separation anxiety disorders, and major depressions make up the majority of cases. It is difficult but possible to diagnose depressive disorders in children with associated organic states.

For children who survive, discharge from the hospital is often marked by ambivalence. The child is then often more dependent on the parent, and may be more demanding. Parents and siblings in turn may resent the child's need for attention, yet are concerned by the risk of precipitating a recurrence. Ideally, the unit or associated outpatient facility is a secure place for the child to return for follow-up visits.

For children whose condition deteriorates, the transition terminal state is often not recognized simultaneously by all. Special sessions maybe needed if the patient dies, so that the donor and the family may ask unresolved questions and be screened for emerging problems.

III. DISEASES TREATED AND THEIR RESPECTIVE TREATMENT PROTOCOLS

A) BMT for Acute Lymphocytic Leukemia (ALL)

I. Background

- Approximately 70% of kids with ALL are cured with conventional chemotherapy. Allogeneic BMT is therefore, usually reserved for patients who fail standard therapy or as initial therapy in those who are considered "very high risk" for relapse.
- BMT is typically used in patients with ALL whose first remissions (CR1) last less than 36 months, namely those who relapse either on therapy or within 6 months of stopping therapy. Historically, these patients only have a 10% cure rate with additional standard chemotherapy vs a 40% cure rate with BMT.
- BMT is particularly indicated if a patient's first marrow remission lasts <18 months because the DFS with chemo in this case is < 5%.
- For those patients with a marrow relapse, it is thought to be important to try to achieve a second remission prior to transplant. This contrasts with AML, in that the disease free survival (DFS) for patients with AML appears to be no different if they are transplanted in second remission or in untreated first relapse.
- For patients who have a late (>18 months on therapy) extramedullary relapse (CNS or testicular) a significant proportion are curable with continued conventional chemotherapy and local radiation therapy. BMT is therefore, typically reserved for patients who develop an early CNS relapse (< 18 months on therapy), a second relapse (extramedullary or systemic) or in patients whose extramedullary relapse occurred in a previously irradiated site.

II. BMT for ALL in first remission (CR1)

Allo-BMT

- Several presenting features of ALL portend a poor prognosis. This is defined by an expected 5 year DFS of $\leq 40\%$. An allo-BMT in CR1 has been proposed for these high risk patients.
- Historically Allo-BMT in first remission ALL has a DFS of between 40-80% with most centers reporting 60%.
- Since there is presently no standard chemotherapy preparative regimen for ALL, total body irradiation (TBI) is usually be used in combination with chemo.
- The eligibility criteria for high-risk disease includes:
 1. cytogenetic abnormalities - t[9;22] (Ph¹ chromosome) and t[4;11] in infants, as well as hypodiploidy or ≤ 44 chromosomes in the patient's leukemia cells

2. infants with MLL gene rearrangement

3. patients with M2 or M3 bone marrows on day 29 - when they had less percent blasts in the marrow on day 14

- Protocols (for high-risk CR1 or more advanced disease):
- COG: P9407: infant ALL
- TP #105: TBI/VP-16 for high-risk disease, matched family member
- IRB# 141-96: MUD/UCBT FTBI/Cytosan (1350 cGy/120 mg/kg) or Bu/Cy/ATG (12 mg/kg/120 mg/kg/90mg/kg)
- IRB# 257-95: UCBT FTBI/Melphalan/ATG (1350 cGy/135 mg/m²/90 mg/kg) or Bu/Mel/ATG Busulfan: < 6 months 1 mg/kg IV q6 x 16 doses; 6 months – 6 years 40 mg/m² PO q6 x 16 doses; > 6 years 1 mg/kg PO q6 x 16 doses – if rejected then Fludara/Melphalan/ATG (125 mg/m²/135 mg/m²/90 mg/kg), if non-engrafted Cy/ATG (60 mg/kg/90 mg/kg then 10 mg/kg x 2)
- IRB# 281-00: mini-allo , matched family member Bu/Fludarabine/ATG (8 mg/kg/180 mg/m²/40 mg/kg) and Tacrolimus or Fludara/TBI (90 mg/m²/200cGy) and CsA/MMF

B) BMT for Acute Myeloid Leukemia (AML)

I. Background

- Historically there is a DFS of approximately 50% for patients treated with standard chemotherapy alone, providing they do not have specific high-risk features such as monosomy 7.
- No study has ever shown a survival advantage for standard chemotherapy over BMT (several have shown equivalent survivals); whereas many have shown the converse. As such, if a matched family is available BMT is CR1 is the treatment of choice but alternative donor BMT such as a MUD or UCBMT is reserved only for patients with monosomy 7 or for those who fail conventional therapy.

II. BMT for AML

Allo-BMT

- The DFS for patients transplanted in CR1 approaches 70% and in CR2 is approximately 40%.
- In an attempt to decrease the relapse rate, Seattle dose escalated TBI with limited success. They saw a decreased relapse rate but an increased toxic death rate; thus no overall improvement in the DFS was seen.
- COG: None open at this time so we use TP #107
- TP #107: Bu/Cy (16 mg/kg/200 mg/kg), “long MTX” only for GVHD prophylaxis, matched family member, if high-risk can use TP #105: TBI/VP-16
- IRB# 141-96: MUD/UCBT FTBI/Cytosan (1350 cGy/120 mg/kg) or Bu/Cy/ATG (12 mg/kg/120 mg/kg/90mg/kg)

- IRB# 257-95: UCBT FTBI/Melphalan/ATG (1350 cGy/135 mg/m²/90 mg/kg) or Bu/Mel/ATG Busulfan: < 6 months 1 mg/kg IV q6 x 16 doses; 6 months – 6 years 40 mg/m² PO q6 x 16 doses; > 6 years 1 mg/kg PO q6 x 16 doses – if rejected then Fludara/Melphalan/ATG (125 mg/m²/135 mg/m²/90 mg/kg), if non-engrafted Cy/ATG (60 mg/kg/90 mg/kg then 10 mg/kg x 2)
- IRB# 281-00: mini-allo , matched family member Bu/Fludarabine/ATG (8 mg/kg/180 mg/m²/40 mg/kg) and Tacrolimus or Fludara/TBI (90 mg/m²/200cGy) and CsA/MMF

C) BMT for Chronic Myelogenous Leukemia (CML)

I. Background

- Prior to Gleevec, without BMT CML was a fatal disease with a median survival of 4 years.
- It is caused by the Ph¹ chromosome which is a translocation between chromosome 9 and 22 [t(9;22)] which codes for bcr/abl (a fusion protein), that is involved in tumorigenesis.
- CML has 3 distinct disease phases:
 - 1) chronic phase (CP) - this phase has a median duration of 3 years, and is by definition easily controlled with oral Hydroxyurea and/or sub-cutaneous α -interferon
 - 2) accelerated phase (AP) - noted by increasing counts; > 10% blasts; > 20% basos and eos; an enlarging spleen; additional chromosomal abnormalities; extramedullary disease, as well as the need for increasing doses of chemotherapy to maintain disease control. This phase can be of very short duration or absent altogether.
 - 3) blast crisis (BC) - median survival 2-5 months. Blast crisis is clinically like acute leukemia, most commonly of the myeloid type but can also be of lymphoid type as well.

Allo-BMT

- Historically there is a DFS of 60-95% with a RR of 5-20%.
- There are several prognostic features for BMT:
 - 1) stage of disease - patients transplanted in CP do better than those in AP who, in turn, do better than those in BC
 - 2) age at transplant - patients less than 30 years old do better
 - 3) interval from diagnosis to BMT - patients transplanted within 1 year of diagnosis and especially if within 6 months do significantly better than those transplanted later in CP
 - 4) previous Busulfan therapy - patients previously treated with Busulfan do worse because they have a higher toxic death rate after BMT
- **Syngeneic or T-depleted transplants:** these patients have a very high RR \square 60%. This strongly suggests that GVHD is "not all bad" because GVHD most likely causes (or is associated with) a graft vs leukemia (GVL) effect that is thought to be important in

preventing relapse. Syngeneic and T-depleted transplants have very little or no GVHD and therefore, no GVL effect.

- Protocols
- TP #105: TBI/VP-16 for accelerated phase or blast crisis, matched family member
- TP #109: Ara-C/Cy/TBI (500 mg/m²/120 mg/kg/550 cGy) matched family member
- IRB# 141-96: MUD/UCBT FTBI/Cytosan (1350 cGy/120 mg/kg) or Bu/Cy/ATG (12 mg/kg/120 mg/kg/90mg/kg)
- IRB# 257-95: UCBT FTBI/Melphalan/ATG (1350 cGy/135 mg/m²/90 mg/kg) or Bu/Mel/ATG Busulfan: < 6 months 1 mg/kg IV q6 x 16 doses; 6 months – 6 years 40 mg/m² PO q6 x 16 doses; > 6 years 1 mg/kg PO q6 x 16 doses – if rejected then Fludara/Melphalan/ATG (125 mg/m²/135 mg/m²/90 mg/kg), if non-engrafted Cy/ATG (60 mg/kg/90 mg/kg then 10 mg/kg x 2)
- IRB# 281-00: mini-allo , matched family member Bu/Fludarabine/ATG (8 mg/kg/180 mg/m²/40 mg/kg) and Tacrolimus or Fludara/TBI (90 mg/m²/200cGy) and CsA/MMF

D) BMT for Non-Hodgkin's and Hodgkin's Lymphoma

1. Background

- The majority of pediatric patients with lymphoma, even those with advanced disease are cured with conventional chemotherapy.
- BMT is therefore reserved for those patients who fail standard front line therapy.

II. BMT for patients with recurrent lymphoma

- The major determinant affecting outcome for pediatric patients who undergo a BMT, is whether or not they have therapy responsive disease. For those patients with responsive disease, the chances for cure with BMT approach 40-60%; whereas for patients who have refractory disease, only 10-15% will be long term disease free survivors.
- Our approach to these patients has been to virtually always recommend auto-BMT for pediatric patients with Hodgkin's disease (HD). We reserve allo-transplant for those patients with evidence of myelodysplasia (from previous MOPP therapy) or for those with refractory disease or bone marrow involvement.
- Conversely, our approach to pediatric patients with non-Hodgkin's lymphoma (NHL) is in general to recommend allo-BMT if possible. This is because pediatric patients invariably have high grade lesions in which a GVL affect appears to be important in preventing relapse. Moreover, young patients in general, tolerate the allo procedure better than adults.
- Protocols:
- TP #111: Cy/Thiotepa/Carbo (6000 mg/m²/500 mg/m²/800 mg/m²), auto PBSCs
- IRB #119: Bu/VP-16/Cy (12 mg/kg/40 mg/kg/120 mg/kg), auto PBSCs
- IRB# 141-96: MUD/UCBT FTBI/Cytosan (1350 cGy/120 mg/kg) or Bu/Cy/ATG (12 mg/kg/120 mg/kg/90mg/kg)

E) **BMT for High Risk Solid Tumors**

1. **Ewing's Sarcoma**

I. **Background**

- Ewing's sarcoma is the second most common malignant bone tumor (after osteosarcoma) in childhood.
- It is associated with t(11;22) or a variant of this translocation in the tumor cells.
- It is a small round blue cell tumor of childhood which includes: leukemia/lymphoma, Ewing's sarcoma/Primitive neuroectodermal tumor (PNET), rhabdomyosarcoma, neuroblastoma, medulloblastoma, and retinoblastoma.
- 12B7 - this is a monoclonal Ab to CD99 that recognizes most Ewing's tumors, and is therefore very useful in making the diagnosis.
- Approximately 25% of patients present with metastases at diagnosis, primarily to the lung but also to bone and bone marrow.
- Conventional chemotherapy (Ifosphamide/VP-16/Vincristine/ Actinomycin D/Cytoxan/Adriamycin) can cure up to 70% of patients with non-metastatic disease who have small primary tumors (< 8 cm in diameter).
- For patients with large primary tumors or who have lung metastases only, approximately 20% of these patients may be cured with conventional therapy alone. However, in patients who relapse early (< 2 years from diagnosis) or who have multifocal bone disease only 5% or less of these patients are curable with standard therapy.

II. **BMT for Ewing's Sarcoma**

- **literature review:** The problem with the Ewing's sarcoma literature is the reports are mainly single institution studies with short follow-up, that include a selected group of patients, that use various reinduction and preparative regimens, which makes it difficult to accurately interpret the data. What appears to be true however, is that auto-BMT likely offers as good or possibly higher DFS for these patients versus those treated with conventional therapy alone. The DFS ranges from 20-65% with an average of 45% at 2 years for patients transplanted either in first remission or in second remission.
- **European Bone Marrow Transplant Registry (EBMTR) data:** this is pooled data from many centers, that reports a 2-3 year DFS of 24% for patients grafted in CR1 and 30% for those in CR2 (sensitive relapse) vs 8% for those in resistant relapse.
- Protocol:
- TP #122: VP-16/Cy/TBI (1800 mg/m²/3600 mg/m²/1200 cGy) for high-risk or recurrent disease

2. **Rhabdomyosarcoma**

1. **Background**

- Rhabdomyosarcoma is the most common soft tissue sarcoma in pediatrics.
- It is the sixth most common pediatric tumor after leukemia, CNS tumors, lymphoma, neuroblastoma, and Wilm's tumor.
- The majority of patients with non-metastatic disease are cured with conventional therapy versus less than 30% of patients with metastatic disease.

2. **BMT for Rhabdomyosarcoma**

- **literature review:** The literature reveals that auto-BMT has been performed fewer times than for Ewing's. Single institution studies reveal DFS for patients transplanted in CR1 to be 25-35%, and near 0% if transplanted after disease progression.
- Protocol:
- TP #122: VP-16/Cy/TBI (1800 mg/m²/3600 mg/m²/1200 cGy) for high-risk or recurrent disease

3. **Neuroblastoma**

I. **Background**

- Neuroblastoma is the most common malignancy in infants.
- There are approx. 550 cases reported per year to the COG.
- It accounts for at least 15% of all cancer related deaths in kids.
- The prognosis is based on patient age, disease stage, and certain biologic factors such as multiple copies of the n-myc oncogene, and hypodiploid tumor cells (< 46 chromosomes).
- Poor risk patients are those older than 1 year, with metastatic disease, multiple copies of n-myc, and hypodiploid tumors.
- Conventional chemotherapy and surgery cure the majority of low and intermediate risk patients, but there has been no real impact on the DFS for Stage IV patients in the past 20 years. Only approximately 15% of these high risk patients are cured with conventional therapy and for this reason the use of auto-BMT has been explored.

II. BMT for Neuroblastoma

- There is no "standard preparative regimen" although most experience is with melphalan with or without other chemotherapy combined with TBI.
- Not only has no regimen proven to be best, but it is also not clear if TBI is needed. It does appear that local XRT to known sites of disease is important to prevent local relapse, however.
- Another controversy is whether or not it is necessary to purge the harvested stem cells and the current COG is studying this question.
- Interestingly, auto BMT appears to be better than allo BMT: there is a lower toxic death rate (8% for auto vs 20% for allo) as well as a trend to a lower relapse rate (30% for auto vs 50% for allo) therefore, the trend towards overall DFS is higher for auto-BMT than for allo-BMT (55% vs 30%).
- There are several factors found not to be prognostic in patients who have received an auto-BMT for neuroblastoma. These include: stage, tumor size, number of mets, n-myc amplification, age, or the induction chemo used. There was, however, a trend to poorer survival in patients who had bone and bone marrow mets.
- Conversely, there are several factors found to be prognostic in these patients: a complete surgical resection at diagnosis is associated with a better outcome (if patients were initially a surgical CR they had a 60% DFS, and if not, they had a 30% DFS) - it is unclear why this is so. Having bone marrow involvement at the time of harvest is a bad prognostic factor (all patients with >400 tumor cells in their BM at the time of harvest relapsed). Time from diagnosis to BMT was prognostic in that patients transplanted within 5-7 months of diagnosis did better. Lastly, disease status at BMT was prognostic, patients in CR or very good partial remission (VGPR) at BMT had a DFS of 50%, whereas, patients in partial remission (PR) at BMT had a DFS of 25%.
- The sites of relapse after BMT were (in order of incidence) - primary site, BM, bone, liver, lung, orbit, CNS. It is clear that we need to improve our preparative regimens since the primary site of disease is the number one site of relapse.
- Overall, BMT does appear to improve the DFS for patients older than 2 years old who have metastatic disease, as well as those who have bone mets, and those whose tumors have n-myc amplification. All of these patients have a < 10% chance of DFS with standard therapy alone.
- Protocols:
- COG A3973: 6 cycles of chemo – 2 cycles of VCR, Cytosin, Dox, followed by PBSC collection (randomized to purged or not) followed by alternating Cisplatin/VP-16 and VCR, Cytosin, Dox x 3 cycles then surgery then VCR, Cytosin, Dox then BMT with Melphalan 70 mg/m²/day x 3, VP-16 338 mg/m²/day x 4, Carboplatin 425 mg/m²/day x 4 and G-CSF, followed by local XRT (2100 cGy to primary site regardless of resection and to all metastatic sites that have not improved by bones scan or MIBG positivity) and Cis-RA 80 mg/m²/dose

bid for 2 weeks on and 2 weeks off x 6 cycles.

- TP #104: Tandem BMT Carbo/VP-16/Cy (2000 mg/m²/2400 mg/m²/120 mg/kg) then Thiotepa/Cy (900 mg/m²/6000 mg/m²) followed by local XRT, high-risk or recurrent disease

4. Recurrent Wilm's Tumor

I. Background

- The majority of all patients with Wilm's tumor are cured by conventional therapy which includes surgery, chemotherapy, and radiation therapy for patients with advanced disease.
- Of those patients that relapse, approximately 1/3 are still curable with salvage chemotherapy.

II. BMT for Recurrent Wilm's tumor

- Nebraska transplanted 12 patients with recurrent Wilm's tumor using a preparative regimen consisting of VP-16, Thiotepa, and Cytosin. 8 patients are disease free with short follow-up: 4 patients relapsed at +3, +4, +8, and +18 months post-BMT.
- **CCG 4921:** under this protocol relapsed patients are classified into low and high risk groups and given reinduction chemotherapy accordingly.
- Low risk patients: those whose initial disease was stage I or II; who received < 3 drugs previously and no prior radiation therapy; who relapsed ≥ 6 months after diagnosis; and whose tumors have favorable histology.
- High risk patients have 1 or more exceptions to the above.
- For patients in the above 2 groups who do not go into complete remission after 3 induction cycles, their bone marrow is harvested (PBSCs must be used and not marrow for patients with BM involvement). PBSCs in addition to bone marrow can be used at the investigator's discretion, in patient's without marrow disease.
- After stem cell harvest the patient receives consolidative therapy with local radiation therapy and conventional chemo followed by auto-BMT.
- The preparative regimen is VP-16 1800 mg/m² x 1 day by continuous infusion, Thiotepa 300 mg/m² x 3, and Cytosin 50 mg/kg x 4 with Mesna 50 mg/kg/day by continuous infusion which is completed 24 hours after the Cytosin.
- The supportive care guidelines include supplemental IV IgG (in addition to other standard institutional guidelines).
- Other protocol:
- TP #122: VP-16/Cy/TBI (1800 mg/m²/3600 mg/m²/1200 cGy) for high-risk or recurrent disease

5. Brain Tumors

I. Background

- It has previously been shown that chemotherapy improves the DFS for patients with high grade brain tumors over that using radiation therapy alone.
- **CCG -943:** compared chemo + XRT to XRT without chemo and saw a 46% 5 year DFS for the combination vs 18% for XRT alone.
- **CCG 945:** studied "8 in 1" (8 drugs in one day) and found that it added nothing to standard therapy. It was also found that patients who had < 90% surgical resection did poorly, and of those who received a biopsy only, all died except 1.

II. BMT for brain tumors

- Previous trials of ABMT for recurrent brain tumors showed responses only in patients with recurrent glioblastomas, anaplastic astrocytomas, and medulloblastomas.
- Protocols:
 - TP #: Melphalan/Cy (6000 mg/m²/ 180 mg/m²), newly diagnosed high-risk disease
 - TP #: Thiotepa/VP-16/Carbo (900 mg/m²/750 mg/m²/calculated by CrCl daily), for advanced disease (NYU protocol)
 - TP #120: 4 cycles of Cisplat/VCR/Cy (75 mg/m²/1.5 mg/m² x 2, 4000 mg/m²), for medulloblastoma or supratentorial PNET

F) BMT for Aplastic Anemia

I. Background

- Patients with severe aplastic anemia (ANC < 500, platelets < 20, reticulocyte counts < 1% with a hypoplastic marrow) have a DFS of 10-20% at 6 months. One should therefore perform a matched sib BMT in these patients as quickly as possible. If there is no matched sibling than alternative donor BMT is reserved for a failure to respond to immunosuppressive therapy.

II. BMT for Idiopathic Aplastic Anemia

- Historically the DFS for allo-BMT is between 60-95%.
- Patient survival has improved as a result of effective prevention of rejection, GVHD, and interstitial pneumonitis.
- Protocols:
 - IRB #589-94: IBMTR randomized Cy (200 mg/m²) vs Cy/ATG, matched sib - closed
 - IRB #252-00: High-dose Cy (200 mg/m²) without BMT
 - TP #121: High-dose Cy with BMT, matched sib
 - IRB #223-98: Cy/ATG/TBI (200 mg/kg/90 mg/kg/200 cGy for MUD/ 400 cGy for

mismatched unrelated) and Tacrolimus/MTX

- IRB# 257-95: UCBT Cy/ATG/TLI (200 mg/kg/90 mg/kg/750 cGy)
- IRB# 281-00: mini-allo , matched family member Bu/Fludarabine/ATG (8 mg/kg/180 mg/m²/40 mg/kg) and Tacrolimus or Fludara/TBI (90 mg/m²/200cGy) and CsA/MMF

G) BMT for Other Disorders

I. Fanconi's Anemia – patients with FA do not repair cellular damage normally (they have a very high-risk of fatal VOD) and therefore they require preparative regimens of significantly less intensity than other patients with aplastic anemia.

- IRB# 141-96: MUD/UCBT Cy/TG/TBI (40 mg/kg/62.5 mg/kg/500 cGy)
- IRB# 257-95: UCBT Cy/ATG/TLI

(200 mg/kg/50 mg/kg/500 cGy)

II. Autoimmune Disorders

- TP# 114: Cy (200 mg/kg) without BMT for AIHA, ITP, and autoimmune neutropenia
- IRB# 102-00: Cy/ATG/Methylpred (120 mg/kg/90 mg/kg/1500 mg), auto PBSC for SLE, RA, and systemic sclerosis
- IRB# 281-00: mini-allo , matched family member Bu/Fludarabine/ATG (8 mg/kg/180 mg/m²/40 mg/kg) and Tacrolimus or Fludara/TBI (90 mg/m²/200cGy) and CsA/MMF

III. Sickle Cell Disease

- IRB# 227-96: Matched sib, MUD, or UCBT: Bu/Cy/ATG (16 mg/kg or < 5years 640 mg/m²)/200 mg/kg/90 mg/kg)
- IRB# 141-96: MUD/UCBT FTBI/Cytosan (1350 cGy/120 mg/kg) or Bu/Cy/ATG (12 mg/kg/120 mg/kg/90mg/kg)
- IRB# : Mini-allo BMT for patients aged 3-15 using Fludara 30 mg/m²/day x 3 days, a day of rest then TBI 200 cGY. CsA and MMF x 35 days then taper as GVHD prophylaxis.

IV. Thalessemia

- IRB# 239-94: matched sib/MUD: Bu/Cy/TLI (12 mg/kg/100 mg/kg/400 cGy)
- IRB# 141-96: MUD/UCBT FTBI/Cytosan (1350 cGy/120 mg/kg) or Bu/Cy/ATG (12 mg/kg/120 mg/kg/90mg/kg)

VI. Inborn Errors of Metabolism

- IRB# 72-00: mini-allo matched sib, haplo, MUD, UCBT: if low-risk of rejection Fludara/TBI (90 mg/m²/200 cGy) with FK506/MMF, if at high-risk of rejection or if previously rejected than Fludara/ATG/Bu (180 mg/m²/40 mg/kg/8 mg/kg or if < 6 years 320 mg/m²) with FK506 only
- IRB# 141-96: MUD/UCBT FTBI/Cytosan (1350 cGy/120 mg/kg) or Bu/Cy/ATG (12 mg/kg/120 mg/kg/90mg/kg)

IV. PEDIATRIC DRUG DOSES

TABLE: Pediatric Drug Dosing	
<i>DRUG NAME</i>	<i>DOSE</i>
ANTI-INFECTIVES	
<i>Aminoglycosides</i>	
Amikacin	9 mg/kg/dose IV Q6H (Q8H if on CyA or FK)
Gentamicin	3 mg/kg/dose IV Q6H (Q8H if on CyA or FK)
Tobramycin	3 mg/kg/dose IV Q6H (Q8H if on CyA or FK)
<i>Antifungals</i>	
Amphotericin B	1 mg/kg/dose IV QD
ABLC (Abelcet®)	5 mg/kg/dose IV QD
Caspofungin	50 mg/m ² IV QD (prelim data from study by Walsh et al. per personal communication with Merck)
Griseofulvin	Microsize: 10-20 mg/kg/day divided QD to BID Ultramicrosize: (> 2 yrs) 5 – 10 mg/kg/day divided QD – BID
Itraconazole	Load: 10 mg/kg/day x 3 days Maintenance: 4-6 mg/kg/day (unlabelled use) (other sources recommend 6-7 mg/kg/day?)
<i>Cephalosporins</i>	
Cefazolin (Kefzol®)	75 – 100 mg/kg/day divided Q8H (max 6 gm/day) (for non-CNS infections)
Cefepime	50 mg/kg/dose IV Q8H
Cefotaxime	50 mg/kg/dose IV Q6-8H
Ceftazidime	50 mg/kg/dose IV Q8H (max 6 gm/day)
Ceftriaxone	Non CNS: 50 mg/kg/dose IV QD (may increase dose if PCN-resistant Strep is a concern) CNS: 100 mg/kg/dose IV QD
<i>Beta-Lactams, Miscellaneous</i>	
Aztreonam	90 – 200 mg/kg/day IV divided Q6 – 8H (150-200 mg/kg/day if neutropenic)
Imipenem	60 – 100 mg/kg/day IV

	<i>(restricted?)</i>	divided Q6H OR 3 mos – 3 yrs: 25 mg/kg/dose IV Q6H (max 2 gm/day) > 3 yrs: 15 mg/kg/dose IV Q6H
	Meropenem <i>(restricted?)</i>	> 3 mos, < 50 kg: 20 mg/kg/dose IV Q8H (max 1 gm/dose); CNS: 40 mg/kg/dose IV Q8H (max 2 gm/dose) > 50 kg: 1 gm IV Q8H; CNS: 2 gm IV Q8H
<i>Macrolides</i>		
	Azithromycin	Mycoplasma: 10 mg/kg/dose (max 500mg) PO day 1; 5 mg/kg/dose (max 250 mg) PO QD days 2-5 Pharyngitis: 12 mg/kg/dose days 1-5 (max 500 mg/day)
	Clarithromycin	15 mg/kg/day PO divided BID
<i>Penicillins</i>		
	Amoxicillin	40 mg/kg/day PO divided TID Otitis media: 90 – 100 mg/kg/day PO divided TID
	Amoxicillin/Clavulana te (Augmentin®)	45 mg/kg/day (amoxicillin) PO divided BID
	Oxacillin	Non-CNS: 100-200 mg/kg/day divided Q6H CNS: 200 mg/kg/day divided Q6H
	Penicillin G	100,000 – 250,000 units/kg/day divided Q4H severe infections: 400,000 units/kg/day divided Q4H (max 24 million units/day)
	Penicillin VK	Prophylaxis: (<5 yrs) 125 mg PO BID (> 5 yrs) 250 mg PO BID Treatment: (<12 yr) 25-50 mg/kg/day divided Q6-8H (max 3 gm/day) (> 12 yrs) 125 – 500 mg Q6-8H
<i>Tetracyclines</i>		
	Doxycycline	< 8yrs, < 45 kg: 2-5 mg/kg/day divided QD-BID (max 200 mg/day)

		> 8yrs, > 45 kg: 100 – 200 mg/day divided QD-BID
<i>Miscellaneous Antibiotics</i>		
	Clindamycin	PO: 10-30 mg/kg/day divided Q6H IV: 40 mg/kg/day divided Q6-8H
	Metronidazole	IV: 7.5 mg/kg/dose Q6H PO: 15-35 mg/kg/day divided TID C. diff: 20 mg/kg/day PO divided Q6H (max 2 gm/day)
	Quinupristin/Dalfopristin (Synercid®) (<i>restricted</i>)	7.5 mg/kg/dose IV Q8-H
	Rifampin	10-20 mg/kg/day divided QD – BID
	Vancomycin	Non-CNS: 10 mg/kg/dose IV Q6H CNS: 15-20 mg/kg/dose IV Q6H
<i>Antivirals</i>		
	Acyclovir	Prophylaxis: 125 mg/m ² IV Q6H or 250 mg/m ² PO Q8H Treatment: 250 mg/m ² IV Q8H or 500 mg/m ² PO 5 x/day (500 mg/m ² IV in immunocompromised patient)
	Cidofovir	5 mg/kg IV Q week Also: probenecid 25 mg/kg PO prior to cidofovir, then 10 mg/kg PO 2 hrs and 8 hrs after cidofovir; NS 10 ml/kg IV over 1 hr prior to and immediately following cidofovir
	Foscarnet	CMV: Induction: 60 mg/kg/dose IV Q8H or 90 mg/kg/dose IV Q12H Maintenance: 90-120 mg/kg/dose IV QD Acyclovir-resistant HSV: 40 mg/kg/IV Q8-12H <i>Dose must be adjusted based on renal function</i> Note: Keep pt well-hydrated, use NS if IVF needed, avoid Lasix

	Ganciclovir	Induction: 5 mg/kg /dose IV Q12H Maintenance: 5 mg/kg/dose IV QD <i>Dose must be adjusted based on renal function</i>
	Valacyclovir	Dosing not well-established (500 mg/dose PO TID) Dose = IV acyclovir dose divided by 0.55; give QD – TID based on indication
<i>Fluoroquinolones</i>		
	Ciprofloxacin	PO: 30 mg/kg/day divided BID IV: 20 mg/kg/day divided BID
<i>Sulfonamides</i>		
	Sulfamethoxazole/ Trimethoprim (SMX/TMP)	PO: 8 – 10 mg/kg/day divided BID PCP: 20 mg/kg/day IV or PO divided Q6H
<i>Sulfones</i>		
	Dapsone	1-2 mg/kg/dose PO QD (max 100 mg/day)
BLOOD-RELATED PRODUCTS		
	Aminocaproic Acid (Amicar®)	PO: 100 mg/kg/dose PO Q6-8H (max 6 gm/dose) IV: 100 mg/kg/dose bolus, then infusion of 33 mg/kg/hr (max 1 gm/hr; max 18 gm/m2/day)
	Antithrombin III (AT III)	1 unit/kg increases plasma ATIII levels by 1-2%
	Enoxaparin (Lovenox®)	Dosing not established Prophylaxis: 0.75 mg/kg Q12H (< 2 months) or 0.5 mg/kg/dose Q12H (if 2 mo – 18 yrs) Treatment: 1.5 mg/kg/dose Q12H (<2 months) or 1 mg/kg/dose Q12H (2 mo – 18 yrs)
	FEIBA®	25-100 factor VIII units/kg/dose
	Heparin	50-100 unit/kg IV Q4H OR 50 unit/kg bolus, then 15-25 units/kg/hr CIVI

	Iron Dextran	IV: total dose replacement (preferred) IM: 5-10kg: 50mg (1ml); 10-50 kg: 100 mg (2ml)
	Novoseven®	90 mcg/kg/IV Q2H, with gradual taper off (to Q4H, then Q6h, Q8H, etc.)
	Protamine	Depends on heparin dose; 1 mg neutralizes ~ 100 units heparin; max dose is 50mg
	Warfarin (Coumadin®)	0.05-0.34 mg/kg/day PO; usual maintenance dose is ~ 0.1 mg/kg/day (> 1yr)
CARDIAC		
	Atenolol	1-2 mg/kg/dose PO QD
	Captopril	Infants: 0.15 – 0.3 mg/kg/dose TID; titrate 0.5 – 2 mg/kg/dose PO TID; max 6 mg/kg/day older children: 6.25-12.5 mg/dose TID; max 6 mg/kg/day (up to adult max dose)
	Clonidine	5-10 mcg/kg/day divided Q8-12H; titrate by 25 mcg/kg/day to max of 0.9 mg/day (max 0.3 mg/dose)
	Diazoxide	1-2 mg/kg/dose (max 150 mg) prn; max duration is 10 days
	Labetalol	PO: 4 mg/kg/day divided BID (max 2400 mg/day) IV:0.3-1 mg/kg/dose intermittently; 0.4-1 mg/kg/hr continuous infusion (max 3 mg/kg/hr)
	Nifedipine	Immediate release:0.25 – 0.3 mg/kg/dose PO initially; max 10 mg/dose
ANALGESICS: NSAIDS		
	Ketorolac (Toradol®)	< 6yr: 1 mg/kg/dose IV/IM Q6H prn > 6yr: 0.5 mg/kg/dose IV/IM Q6H prn * max 120 mg/day, max 5 days
	Naproxen	> 2yr: 2.5-7 mg/kg/dose PO Q8-12H (max 10 mg/kg/day)

ANALGESICS: OPIATES

Codeine	Pain: 0.5 – 1 mg/kg/dose IM/PO Q4-6H (max 60 mg/dose) Cough: 1-1.5 mg/kg/day divided Q6H OR 2-6 yrs: 2.5-5mg PO Q4H prn (if normal size/weight) 6-12yrs: 5-10 mg PO Q4H prn(if normal size/weight) > 12 yrs: 10-20 mg PO Q4H prn(if normal size/weight)
Fentanyl	1-2 mcg/kg/dose IV/IM, may repeat Q30-60 min 1-2 mcg bolus, then 0.5 - 1 mcg/kg/hr CIVI
Hydromorphone	Younger children: 0.03 – 0.08 mg/kg/dose PO Q4-6H prn (max 5 mg/dose unless titrating up); 0.015 mg/kg/dose IV Q4-6H prn (older children) 1-4 mg PO Q4H prn; 0.2 – 1 mg IV Q4H prn
Methadone	PO/IM: 0.7 mg/kg/day divided Q4-6H OR 0.1-0.2 mg/kg/dose Q4-12H prn IV: 0.1 mg/kg/dose Q4H x 2- 3 doses, then Q6-12H prn (max 10 mg/dose)
Morphine	0.05 – 0.2 mg/kg/dose IV/IM Q2-4H prn 0.02 – 0.07 mg/kg/hr continuous IV infusion PCA: 0.1 mg/kg loading dose; 0.01 – 0.02 mg/kg/dose PCA (demand) dose; 4 hr lockout ~ 0.08 mg/kg PO: (IR) 0.2-0.5 mg/kg/dose Q4H prn; (SR) 0.3-0.6 mg/kg Q12H ATC
Oxycodone	0.05 – 0.15 mg/kg/dose PO Q4-6H prn OR 6-12 yrs: 1.25 mg Po Q6H prn > 12 yrs: 2.5 PO Q6H prn
Naloxone (Narcan®)	0.1 mg/kg/dose, max single dose – 2 mg (for total reversal)

		(usual adult dose = 0.4 mg)
GI MEDICATIONS		
	Diphenoxylate/Atropine (Lomotil®)	0.3-0.3 mg/kg/day divided BID-QID OR 2-5 yrs: 2mg PO TID (not recommended in < 2yrs) (if normal weight) 5-8 yrs: 2 mg PO QID(if normal weight) 8-12 yrs: 2 mg PO 5x/day(if normal weight)
	Docusate (Colace®)	< 2yr: 25 mg/day PO 2-12yrs: 50 – 150 mg/day PO > 12 yrs: 50 – 300 mg/day PO divided QD – TID
	Loperamide (Imodium®)	2-6 yrs: 1 mg PO TID in 1st day, then 0.1 mg/kg/dose (max 1 mg) prn 6-8 yrs: 2 mg PO BID in 1st day, then 0.1 mg/kg/dose (max 2 mg) prn 8-12 yrs: 2 mg PO TID in 1st day, then 0.1 mg/kg/dose (max 2 mg)prn Chronic diarrhea: 0.08-0.24 mg/kg/day divided BID-TID; max 2 mg/dose
	Simethicone	20-40 mg PO prn
	Mag Citrate	< 6yrs: 0.5 ml/kg/dose PO 6-12yrs: 80 – 120 ml/dose PO > 12 yrs: 120 – 240 ml/dose PO
	Mag Oxide	400-800 mg PO Qd-QID
	Mag Sulfate	25 – 50 mg/kg IV Q6H as needed 100-200 mg/kg/dose PO QID (diarrhea may be greater vs. mag oxide)
	Metoclopramide	0.1-0.2 mg/kg/dose up to QID (max 0.5 mg/kg/day)
	Octreotide	Not clearly defined 1 – 10 mcg/kg IV/SC Q12H; titrate 0.3 mcg/kg/dose at 3 day intervals
	Omeprazole	Not clearly defined 0.6 – 0.7 mg/kg/day, titrate up to 3.5 mg/kg/day; normal dose is 1 – 1.5 mg/kg/day

	Ondansetron	0.15 mg/kg/dose IV OR 4-8 mg PO
	Pantoprazole	Not clearly defined (1 mg/kg/dose PO/IV QD?)
	Promethazine	0.25-1 mg/kg/dose IV/PO Q4-6H prn
	Ranitidine	PO: 1.25-2.5 mg/kg/dose PO BID (max 300 mg/day) IV: 0.75-1 mg/kg/dose IV Q6-8H (max 400 mg/day)
	Senna	For kids > 27 kg Tabs: 1 tab QD, max 2 tabs BID Syrup: 1mo-1yr: 1.25 – 2.5 ml QHS, max 2.5 ml BID 1-5 yrs: 2.5-5 ml QHS, max 5 ml BID 5-15 yrs: 5-10 ml QHS, max 10 ml BID
	Ursodiol (Actigall®)	10-20 mg/kg/day PO divided Q8-12H
IMMUNOSUPPRESSIVES		
	ATG	Atgam®: varies; 10-30 mg/kg/dose; requires test dose Thymoglobulin®: varies; 1.5 mg/kg/dose
	Cyclosporine	PO: 3 mg/kg/dose Q8H IV: 1 mg/kg/dose Q8H
	Daclizumab (Anti-IL2)	1 mg/kg IV days 1, 4, 8, 15, 22 of therapy
	Infliximab (Anti-TNF)	Dose/Use not well-established
	Mycophenolate mofetil (CellCept®)	600 mg/m ² /dose PO or IV Q12H
	Tacrolimus (FK506)	PO: 0.04 mg/kg/dose Q8H (may be Q12H if > 8 yrs) IV: 0.04 mg/kg/day continuous infusion
MISCELLANEOUS MEDICATIONS		
	Acetaminophen	10-15 mg/kg/dose PO/PR Q4-6H PRN
	Acetazolamide (Diamox®)	5 mg/kg PO/IV QD OR 150 mg/m ² PO/IV QD
	Diphenhydramine	1 mg/kg/dose PO/IV Q6H prn OR 2-6 yrs: 6.25 mg/dose PO/IV

		Q6H prn (if normal weight for age) 6-12 yrs: 12.5-25 mg/dose PO/IV Q6H prn(if normal weight for age) > 12 yrs: 25-50 mg/dose PO/IV Q6H prn(if normal weight for age)
	Lorazepam	0.05 mg/kg/dose PO/IV Q4H prn (max 2 mg/dose)

Note: Above doses may not necessarily apply to the neonatal population (>2 months). Doses for this population should be verified prior to prescribing.

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