HEMATOPOIETIC CELL TRANSPLANTS - Data CYE 2005- CYE 2008

HCT- Autologous
Bone Marrow
Transplants-
inclusive of
Peripheral stem cells,
bone marrow and
cord blood

AHCCCS Data for Cases Members >21 years

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Note- 2005 a transplant log of all members was not maintained with all data

HCT- Allogeneic
Related Bone
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AHCCCS Data for Cases Members >21 years

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Note- 2005 a transplant log of all members was not maintained
HCT- Allogeneic
Unrelated Bone
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AHCCCS Data for Cases Members >21 years

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Note- 2005 a transplant log of all members was not maintained.

Mortality numbers are tracked by member and reflect the 1st 6 months after transplant.

SUMMARY OF FINDINGS:

Hematopoietic stem cell transplantation (HSCT) is the transplantation of blood stem cells derived from the bone marrow (in this case known as bone marrow transplantation) or blood. Stem cell transplantation is a medical procedure in the fields of hematology and oncology, most often performed for people with diseases of the blood, bone marrow, or certain types of cancer.

With the availability of the stem cell growth factors GM-CSF and G-CSF, most hematopoietic stem cell transplantation procedures are now performed using stem cells collected from the peripheral blood, rather than from the bone marrow. Collecting peripheral blood stem cells[1] provides a bigger graft, does not require that the donor be subjected to general anesthesia to collect the graft, results in a shorter time to engraftment, and may provide for a lower long-term relapse rate.

Hematopoietic stem cell transplantation remains a risky procedure with many possible complications; it has traditionally been reserved for patients with life-threatening diseases. While occasionally used experimentally in nonmalignant and nonhematologic indications such as severe disabling auto-immune disease and cardiovascular disease, the risk of fatal complications appears too high to gain wider acceptance.
Two Types of Bone Marrow Transplants

*Autologous bone marrow transplant:* The donor is the person him/herself.

*Allogenic bone marrow transplant:* The donor is another person whose tissue has the same genetic type as the person needing the transplant (recipient). Because tissue types are inherited, similar to hair or eye color, it is more likely that the recipient will find a suitable donor in a brother or sister. This, however, happens only 25 to 30 percent of the time.

If a family member does not match the recipient, the National Marrow Donor Program Registry database is searched for an unrelated individual whose tissue type is a close match. It is more likely that a donor who comes from the same racial or ethnic group as the recipient will have the same tissue traits. The chances of a minority person in the United States finding a registry match are lower than that of a white person.

Sources of Bone Marrow Stem Cells

There are three kinds of bone marrow transplants:

Autologous bone marrow transplant. "Auto" means "self." Stem cells are taken from the patient before the patient gets chemotherapy or radiation treatment. When chemotherapy or radiation is done, the patient gets their stem cells back. This is called a "rescue" transplant.

Allogeneic bone marrow transplant. "Allo" means "other." Stem cells come from another person, who is called a donor. Donor stem cells come from the donor's bone marrow or their blood. Most times, a donor must have the same genetic typing as the patient, so that their blood "matches" the patient’s. Special blood tests will tell whether a possible donor is a good match for the patient. A patient’s brothers and sisters have the highest chance of being a good match. But, sometimes parents and children of the patient and other relatives may be matches. Donors who are not related to the patient may be found through national bone marrow registries. These are lists of people who have offered to be donors.

Umbilical cord blood transplant. Stem cells are taken from an umbilical cord right after delivery of an infant. The stem cells are tested, typed, counted, and frozen and kept until they are needed for transplant. A patient can use their own cord blood if arrangements are made at birth to store the blood for later use.

Conditioning regimens

Myeloablative transplants

The chemotherapy or irradiation given immediately prior to a transplant is called the conditioning or preparative regimen, the purpose of which is to help eradicate the patient's disease prior to the infusion of HSC and to suppress immune reactions. The bone marrow can be *ablated* with dose-levels that cause minimal injury to other tissues. In allogeneic transplants a combination of cyclophosphamide with busulfan or total body irradiation is commonly employed. This treatment also has an immunosuppressive effect which prevents rejection of the HSC by the recipient's immune system. The post-transplant prognosis often includes acute and chronic graft-versus-host disease which may be life-threatening; however in certain leukemias this can coincide with protection against cancer relapse owing to the *graft versus tumor* effect. *Autologous* transplants may also use similar conditioning regimens, but many other chemotherapy combinations can be used depending on the type of disease.
Non-myeloablative (or "mini") allogeneic transplants
This is a newer treatment approach using lower doses of chemotherapy and radiation which are too low to eradicate all of the bone marrow cells of a recipient. Instead, non-myeloablative transplants run lower risks of serious infections and transplant-related mortality while relying upon the *graft versus tumor* effect to resist the inherent increased risk of cancer relapse. Also significantly, while requiring high doses of immunosuppressive agents in the early stages of treatment, these doses are less than for conventional transplants. This leads to a state of mixed chimerism early after transplant where both recipient and donor HSC coexist in the bone marrow space.

Decreasing doses of immunosuppressive therapy then allows donor T-cells to eradicate the remaining recipient HSC and to induce the graft versus tumor effect. This effect is often accompanied by mild graft-versus-host disease, the appearance of which is often a surrogate for the emergence of the desirable graft versus tumor effect, and also serves as a signal to establish an appropriate dosage level for sustained treatment with low levels of immunosuppressive agents.

Because of their gentler conditioning regimens, these transplants are associated with a lower risk of transplant-related mortality and therefore allow patients who are considered too high-risk for conventional allogeneic HSCT to undergo potentially curative therapy for their disease. These new transplant strategies are still somewhat experimental, but are being used more widely on elderly patients unfit for myeloablative regimens and for whom the higher risk of cancer relapse may be acceptable.

**Criteria for listing:**
Hematopoietic Cell Transplants (HCT) is indicated as the standard of care for multiple diagnoses. The American Society for Blood and Marrow Transplantation (ASBMT) has issued specific evidenced based medical guidelines for the treatment of certain diseases. HCT is primarily reserved for life-threatening illnesses that acquired (e.g. malignancies) or congenital disorders, as listed below:

**Conditions treated with bone marrow or HSC transplantation**

**Acquired**
- Malignancies
- Hematological
- Leukemias
- Acute lymphoblastic leukemia (ALL)
- Acute myelogenous leukemia (AML)
- Chronic lymphocytic leukemia (CLL)
- Chronic myelogenous leukemia (CML), accelerated phase or blast crisis
- Lymphomas
- Hodgkin's disease
• Non-Hodgkin's lymphoma
• Myelomas
• Multiple myeloma (Kahler's disease)
• Solid tumor cancers
• Neuroblastoma
• Demplastic small round cell tumor
• Ewing's sarcoma
• Choriocarcinoma
• Hemotoloical disorders
• Phagocyte disorders
• Myelodysplasia

Anemias
• Paroxysmal nocturnal hemoglobinuria (PNH; severe aplasia)
• Aplastic anemia
• Acquired pure red cell aplasia
• Myeloproliferative disorders
• Polycythemia vera
• Essential thrombocytosis

Metabolic disorders
• Amyloidoses
• Amyloid light chain (AL) amyloidosis
• Environmentally-induced diseases
• Radiation poisoning

Congenital
• Lysosomal storage disorders
• Lipidoses (disorders of lipid storage)
• Neuronal ceroid lipofuscinoses
• Infantile neuronal ceroid lipofuscinosis (INCL, Santavuori disease)
• Jansky-Bielschowsky disease (late infantile neuronal ceroid lipofuscinosis)
• Sphingolipidoses
• Niemann-Pick disease
• Gaucher disease
• Leukodystrophies
• Adrenoleukodystrophy
• Metachromatic leukodystrophy
• Krabbe disease (globoid cell leukodystrophy)
• Mucopolysaccharidoses
  • Hurler syndrome (MPS I H, α-L-iduronidase deficiency)
  • Scheie syndrome (MPS I S)
  • Hurler-Scheie syndrome (MPS I H-S)
  • Hunter syndrome (MPS II, iduronidase sulfate deficiency)
  • Sanfilippo syndrome (MPS III)
  • Morquio syndrome (MPS IV)
  • Maroteaux-Lamy syndrome (MPS VI)
  • Sly syndrome (MPS VII)
  • Glycoproteinoses
  • Mucolipidosis II (I-cell disease)
  • Fucosidosis
  • Aspartylglucosaminuria
  • Alpha-mannosidosis

Other
• Wolman disease (acid lipase deficiency)
• Immunodeficiencies
• T-cell deficiencies
• Ataxia telangiectasia
• DiGeorge syndrome
• Combined T- and B-cell deficiencies
• Severe combined immunodeficiency (SCID), all types
• Well-defined syndromes
• Wiskott-Aldrich syndrome
• Phagocyte disorders
• Kostmann syndrome
• Shwachman-Diamond syndrome
• Immune dysregulation diseases
• Griscelli syndrome, type II

Innate immune deficiencies
• NF-Kappa-B Essential Modulator (NEMO) deficiency (Inhibitor of Kappa Light Polypeptide Gene Enhancer in B Cells Gamma Kinase deficiency)
• Hematologic diseases

Hemoglobinopathies
• Sickle cell disease
• β thalassemia major (Cooley's anemia)
• Anemias
  • Aplastic anemia
  • Diamond-Blackfan anemia
  • Fanconi anemia
  • Cytopenias
  • Amegakaryocytic thrombocytopenia
  • Hemophagocytic syndromes
  • Hemophagocytic lymphohistiocytosis (HLH)

**Malignancies**
• Solid tumor cancers
• Neuroblastoma

A review of the current literature defines treatment options in terms of the type of underlying disorder. The majority of these disorders affect children primarily.

Indications for Adults are:

**Autologous** transplants are available for the following diseases:
• Acute myelogenous leukemia, in complete remission
• Acute lymphoblastic leukemia, in complete remission
• Relapsed or primary refractory Hodgkin’s disease
• Relapsed, low-, intermediate- or high-grade non-Hodgkin’s lymphoma
• Standard risk multiple myeloma
• Selected patients with metastatic breast cancer
• Relapsed germ-cell/testicular tumors
• Primary amyloidosis

**Allogeneic** transplants (HLA-matched sibling and syngeneic) are used for patients with HLA identical family donors or identical twin donors for the following diseases:
• Severe aplastic anemia or paroxysmal nocturnal hemoglobinuria
• Chronic myelogenous leukemia in chronic or accelerated phase
• Myelodysplastic syndromes
• Myelofibrosis
• Acute myelogenous leukemia, in complete remission, early relapse, or refractory disease
• Acute lymphoblastic leukemia, in complete remission or early relapse
• Relapsed or refractory Hodgkin’s and non-Hodgkin’s lymphomas
• High risk multiple myeloma
• Relapsed chronic lymphocytic leukemia
**Mortality and Morbidity:**

Autologous stem cell transplantation (ASCT) is increasingly performed in older adults. Predictors of transplant related mortality (TRM) are not well established in this population. In a study presented and published by the American Journal of Oncology, June 2006, researchers set out to identify characteristics associated with TRM in older adults treated with ASCT. Between July 1990 and July 2005, patients > 60 years of age treated with ASCT records were reviewed. The study looked at 139 patients, the median age was 64.5 (range 60-76.6) years, and 34% were female. Primary diagnoses included non-Hodgkin's lymphoma (55%), multiple myeloma (29%), acute myelogenous leukemia (8%), breast cancer (5%), and Hodgkin's lymphoma (3%). 100 day TRM was 7.9%. The mean time to engraftment (absolute neutrophil count >1000) was 12.2 ± 5.5 days. Complications included bacteremia (26.3%), cardiac events (myocardial infarction, congestive heart failure or arrhythmia) (11.5%), renal failure (7.4%), and respiratory failure (6.7%). Multivariate analysis including age, sex, diagnosis, number of comorbidities, number of medications, congestive heart failure, coronary artery disease, diabetes mellitus, hemoglobin, and creatinine at the time of transplant did not identify any baseline predictors of 100 day TRM (p > .05 for all). Development of renal failure or respiratory failure during transplantation was associated with increased TRM with an odds ratio of 11.2 (CI 2.5, 49.2) and 13.6 (CI 3.0, 62.2) respectively. Peritransplant cardiac events or bacteremia were not associated with increased TRM. The findings are consistent with other studies that have shown that the development of renal failure or respiratory failure is associated with increased TRM in this study. However, age and baseline comorbidities are not predictive of TRM. Future prospective studies should incorporate specific measures of functional and cognitive status which may be more reflective of decreased physiologic reserve in older adults being considered for ASCT.

**Prognosis** in HCT varies widely dependent upon disease type, stage, stem cell source, HLA-matched status (for allogeneic HCST) and conditioning regimen. A transplant offers a chance for cure or long-term remission if the inherent complications of graft versus host disease, immuno-suppressive treatments and the spectrum of opportunistic infections can be survived. In recent years, survival rates have been gradually improving across almost all populations and sub-populations receiving transplants. Mortality for allogeneic stem cell transplantation can be estimated using the prediction model created by Sorror et al., using the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI). The HCT-CI was derived and validated by investigators at the Fred Hutchinson Cancer Research Center (Seattle, WA). The HCT-CI modifies and adds to a well-validated comorbidity index, the Charlson Comorbidity Index (CCI) (Charlson et al.) The CCI was previously applied to patients undergoing allogeneic HCT but appears to provide less survival prediction and discrimination than the HCT-CI scoring.
system. The probability of survival can be calculated using this tool and a decision can be made whether other treatment may provide a better outcome or the patient should be referred for transplant.

http://www.qxmd.com/hematology/Hematopoietic-Cell-Transplantation-Specific-Comorbidity-Index-HCT-CI.php

As many as 40 percent of bone marrow transplant (BMT) patients develop one or more complications that require transfer to an ICU. Respiratory failure is the most common reason for transfer; other reasons include pneumonia, sepsis, mucositis, and intracranial hemorrhage, acute graft-versus-host disease, and cardiac dysfunction, veno-occlusive disease of the liver and adverse reactions to drugs. Twenty-five percent of all BMT recipients ultimately require mechanical ventilation, usually within 60 days of marrow infusion. The presence or absence of respiratory failure is the most significant prognostic feature:

BMT recipients who enter an ICU but do not undergo mechanical ventilation have a mortality rate of approximately 20 percent.

Mechanical ventilation is associated with a poor prognosis. In the largest study reported to date, only 6 percent of 865 BMT recipients treated at the Fred Hutchinson Cancer Research Center in Seattle who required mechanical ventilation survived more than 30 days after extubation. Patients who were ventilated for less than 24 hours were excluded from analysis. This is an important distinction since, in an earlier report from the same center, 27 percent of all patients survived an initial episode of ventilatory support.

Other smaller studies of pediatric and adult BMT recipients requiring mechanical ventilation have reported overall survival rates of 0 to 29 percent. Six-month survival for patients with respiratory failure ranges from 3 to 12 percent. The duration of mechanical ventilation is an uncertain predictor of outcome. Whereas several studies found no association between the duration of mechanical ventilation and the likelihood of survival, others report no long-term survivors among patients who require mechanical ventilation longer than 13 days.

Risk factors for respiratory failure: Several pretransplant risk factors for respiratory failure have been identified. In adults, these include an incomplete match between donor and recipient HLA type (which yielded a respiratory failure risk of 50 percent in one study, and active malignancy at the time of transplantation. In addition, a large prospective cohort study identified abnormal pulmonary function following BMT as a risk factor for nonrelapse mortality. Abnormalities in pulmonary function were common in this population, as 34 percent of the 906 patients studied had restrictive pulmonary defects.

Predicting survival after mechanical ventilation: Studies attempting to identify predictors of mortality once respiratory failure is established in BMT recipients have yielded inconsistent results. The most valuable outcome predictors derive from a 12-year retrospective study of 3635 patients who underwent bone marrow transplantation at the Fred Hutchinson Cancer Research Center in Seattle. There were no survivors among 398 patients who had hypoxemic respiratory failure (FiO2 greater than 0.60 or PEEP
greater than 5 cmH2O after the first 24 hours of mechanical ventilation) if either of the following were present:

- Serum total bilirubin concentration greater than 4 mg/dL and renal insufficiency (serum creatinine concentration greater than 2.0 mg/dL [177 µmol/L])
- A need for more than four hours of vasopressor support (dopamine infusion rate greater than 5 mcg/kg per min)

Other smaller studies have confirmed the adverse effect of combined hepatic and renal dysfunction on survival in this population. Older age, repeated need for mechanical ventilation, and a higher APACHE III score on day one also appear to correlate with mortality. APACHE II scores may not as reliably predict mortality or ICU or hospital length of stay in this population.

Survival does not appear to be affected by sex, indication for BMT, type of graft (autologous versus allogeneic), use of total body irradiation, indication for intubation, parenteral nutrition, blood transfusions, or use of a Swan-Ganz catheter. Graft-versus-host disease is a risk factor for respiratory failure, but does not help predict its outcome.

Patients who require mechanical ventilation longer than 24 hours are likely to die in the hospital (94 percent mortality in the largest series). Prognosis should be reassessed at frequent intervals with particular attention to the development of multiple organ dysfunctions. Data support palliative care exclusively for many critically ill oncology patients who do not progress toward recovery in the first several days of ICU care.

The pulmonary complications of autologous HCT share many of the features associated with allogeneic HCT, but there are also important differences. Cellular interactions between graft and host cells are largely eliminated with autologous transplantation. Thus, graft rejection and graft-versus-host disease are insignificant and do not require prevention or treatment. The net effect is reduced need for pharmacologic immunosuppression after the transplant.

Posttransplant pneumonitis associated with cytomegalovirus (CMV) infection is rarely a problem after autologous transplantation, in contrast to its high incidence after allogeneic transplantation.

Certain other opportunistic infections, such as Toxoplasma gondii, are very rare after autologous transplantation, as opposed to allogeneic transplant patients.

The infectious complications during the first four to six weeks after both allogeneic and autologous transplants are primarily due to bacterial and fungal infections secondary to neutropenia. In addition, intensive treatment of the underlying malignancy with chemotherapy and radiotherapy (particularly to the
chest) predisposes to serious noninfectious posttransplant pulmonary complications, including diffuse alveolar hemorrhage and drug or radiation toxicity.

**Pre-Engraftment Phase:** The major risk factors for infection during the preengraftment period in the first three weeks after HCT are mucositis and cutaneous damage, which disrupt the natural barriers of the skin and mucous membranes, neutropenia with resulting loss of phagocytic abilities, and organ dysfunction.

- **Bacterial infections,** Aerobic gram-positive and gram-negative bacteria account for most documented infections during this granulocytopenic period.
- **Diarrhea** commonly occurs among patients who have undergone HCT due to both infectious and noninfectious agents. The most common cause of infectious diarrhea in patients undergoing HCT is *Clostridium difficile*-associated diarrhea. The frequency of *C. difficile* associated diarrhea is illustrated by a study of 135 HCT patients who developed diarrhea either before or after engraftment and were tested for *C. difficile* toxin A, 21 (16 percent) were positive.
- **Gram-negative infections** may be caused by *Legionella* spp, *Pseudomonas aeruginosa*, *Enterobacteriaceae*, and *Stenotrophomonas maltophilia*, and other bacteria. The most common sites of bacterial infection include those involving the bloodstream and the lungs, eg, bacteremia and pneumonia. Less frequent manifestations include septic shock, the acute respiratory distress syndrome, and neutropenic enterocolitis.
- **Fungal infections,** allogeneic transplant recipients are at a significantly higher risk for fungal infection than those receiving autologous marrow stem cells.
- **Candida,** the introduction of antifungal prophylaxis with triazole antimicrobials, especially fluconazole, has significantly reduced the morbidity and mortality of invasive candidiasis. However, the incidence of infection with triazole-resistant *Candida* spp, such as *C. krusei* and *C. glabrata*, has increased, probably as a result of this prophylaxis. One study of allogeneic HCT recipients who received either 75 days of prophylactic fluconazole or placebo found after eight years of follow-up that the incidence of invasive candidiasis, early and late mortality from candidiasis, and the occurrence of severe gastrointestinal graft-versus-host disease were all higher among placebo recipients compared to those who received lengthy fluconazole. Risk factors for invasive candidiasis include severe neutropenia, use of broad-spectrum antibiotics, organ dysfunction, mucocutaneous damage, and yeast colonization with *Candida* spp. Candidal infections can either be localized (gastrointestinal tract [eg, thrush, esophagitis], or genital area) or disseminated (acute followed in some instances by chronic infection). Skin lesions, usually erythematous and maculopapular in nature, can be the first evidence of disseminated candidiasis.
- **Molds,** infections caused by molds (*Aspergillus, Fusarium, Zygomyces*, and the agents of hyalohyphomycosis and phaeohyphomycosis) may also occur during this phase. Risk factors for non-candidal fungal infections include allogeneic HCT transplantation, positive pretransplant serology for cytomegalovirus (CMV), and delayed engraftment. None of these factors were
independently significant in the autologous recipients. The major clinical manifestation of infection with these molds is pulmonary infection. However, involvement of the sinuses, central nervous system (CNS), and skin may also occur.

- Viral infections, the major viruses encountered during the immediate posttransplant period are herpes simplex virus (HSV) which reactivates and respiratory viruses.
  - Herpes simplex virus, almost all HSV infections in HCT recipients are caused by viral reactivation; thus, only seropositive patients are at risk. The rate of reactivation is more than 70 percent and appears to be comparable after autologous or allogeneic transplantation. The median time to onset of HSV disease is two to three weeks.
  - HSV-1 infections primarily present as severe mucositis and occasionally esophagitis. Rarely, HCT recipients develop HSV-1 viremia, which can lead to secondary viral infection of organs including: the trachea (erosive tracheobronchitis), lungs, liver, CNS, adrenal glands, or gastrointestinal tract. Erosive tracheobronchitis and pneumonitis can also arise via contiguous spread from the oropharynx.
  - Reactivation of HSV-2 infection in the genital or perineal area accounts for only 10 to 15 percent of all HSV infections in HCT patients. Prophylaxis with acyclovir has markedly reduced the incidence of all herpetic infections in transplant recipients.

- Respiratory viruses, the most common respiratory viruses include respiratory syncytial virus (RSV), the parainfluenza viruses, rhinoviruses, and influenza A and B. The frequency and timing of the isolation of these viruses generally reflects the pattern found concomitantly in the community and often varies from year to year. These infections are seen both in allogeneic and autologous recipients. Emerging data also suggest that human metapneumovirus infection needs to be considered in this patient population.

- Infection with RSV occurs in more than 50 percent of HCT recipients but usually is not a severe illness. However, outbreaks of fatal infections have been linked to this virus in transplant recipients. The role of RSV in these fatal outcomes remains to be determined. RSV infections in HCT recipients with RSV infections usually develop upper respiratory tract symptoms (eg, rhinorrhea, sinus congestion, sore throat, and otitis media), which almost always precede lower respiratory tract infection (tracheobronchitis, pneumonia). Transmission of parainfluenza and influenza viruses is by direct droplet spread or aerosolized respiratory secretions. During community outbreaks, influenza, especially type A, and parainfluenza viruses have been reported as a frequent cause of severe and fatal pneumonia in HCT recipients. The exact role played by these viruses in these fatal infections is unclear.
Immediate Post-Engraftment Phase: The major risk factors for infection during the immediate postengraftment period three weeks to three months after HCT are mucositis and cutaneous damage, similar to preengraftment, but also cellular immune dysfunction, immunomodulating viruses, hyposplenism, decrease in opsonization, and diminished reticuloendothelial function. For allogeneic HCT recipients, additional risk factors include acute graft versus host disease (GVHD) and its therapy.

- Bacterial infections. Bacterial pathogens deserving special attention during this period are Listeria monocytogenes and Legionella pneumophila.
- Fungal infections — Invasive aspergillosis can occur among both allogeneic and autologous HCT recipients although the incidence is more frequent among the former (5 to 30 versus 1 to 5 percent). The median time of onset of aspergillosis is 6 to 12 weeks after transplantation. Risk factors for aspergillosis include older age, the presence and severity of GVHD, corticosteroid therapy, graft failure, diagnosis other than chronic myelogenous leukemia, and advanced cancer at transplantation. There has been increasing recognition of the less common but fatal opportunistic mycoses in transplant recipients, including those caused by Fusarium spp, the Zygomycetes, resistant species of Candida, Pseudallescheria boydii (also known as Scedosporium apiospermum, which is the asexual form of P. boydii), and others. The clinical features of these infections often mimic aspergillosis, although fusariosis has some unique manifestations, which include skin lesions and bloodstream infections.
- Chronic disseminated candidiasis is now rarely seen in HCT recipients since the introduction of triazole prophylaxis. The development of fever, abdominal symptoms, and increasing alkaline phosphatase in a patient who has recently recovered from neutropenia and had not received appropriate antifungal prophylaxis should prompt an investigation for hepatosplenic candidiasis.
- Pneumocystis carinii (jirovecii) pneumonia, the median time to onset of PCP is nine weeks after HCT. However, this pathogen now accounts for less than 1 to 2 percent of pneumonias in transplant recipients with routine use of effective chemoprophylaxis.
- Viral infections. Immunomodulating viruses as well as viruses encountered in the community play a role in viral infections in the immediate postengraftment period.
  - Cytomegalovirus, before the routine use of prophylactic regimens, CMV seropositive allogeneic HCT recipients had a 70 to 80 percent risk of reactivation of this virus, and one-third of these patients developed CMV disease. By comparison, CMV reactivation occurred in only 40 percent of autologous or syngeneic HCT recipients; CMV disease, mainly pneumonia, evolved in fewer than 5 percent of these patients. The risk of acquiring CMV from either blood transfusion or seropositive marrow in CMV seronegative HCT recipients was also approximately 40 percent.
  - Risk factors for symptomatic CMV disease include CMV seropositive recipient, high titer of virus, allogeneic HCT especially from a
matched unrelated donor (MUD), advanced age, use of total body irradiation for conditioning, acute GVHD, and the use of CD34+ selected allogeneic HCT. There does not appear to be a difference between the incidences of CMV disease after allogeneic bone marrow transplantation compared with allogeneic peripheral blood transplantation.

- One study found an increased mortality rate from both bacterial and fungal infections in CMV-seronegative HCT recipients from a CMV-seropositive donor, even after controlling for neutropenia due to ganciclovir and the occurrence of CMV disease. The cumulative mortality at one year after HCT was 18.3 and 9.7 percent for CMV-seronegative recipients of HCT from a CMV-seropositive donor and seronegative recipients from seronegative donors, respectively.

- Human herpes viruses 6, 7, and 8 — Human herpesvirus-6 (HHV-6) reactivation has been documented in 40 to 60 percent of HCT recipients, usually three weeks after transplantation. However, the clinical significance of this reactivation remains to be determined. Clinical syndromes associated with HHV-6 reactivation include rash, fever, interstitial pneumonitis, encephalitis, and bone marrow suppression.

- Epstein-Barr virus, Primary EBV infection presenting with pneumonia was reported in a HCT recipient one month following transplantation. The virus must have been transmitted by the donor's bone marrow as the transplant recipient had negative serologic tests for EBV before transplantation and the donor's bone marrow was positive for EBV.

- Adenovirus, Reactivation of adenovirus infection occurs in greater than 80 percent of autologous and allogeneic HCT recipients but causes severe disease in fewer than two percent. The timing of reactivation differs for children and adults. Adenovirus reactivation develops within 30 days in children but typically more than 90 days following transplantation in adults.
  - There are four clinically significant adenoviral syndromes: pneumonitis, nephritis, diarrhea and hemorrhagic colitis, and hemorrhagic cystitis. Disseminated disease with multiorgan failure can also occur. Asymptomatic nasopharyngeal carriage and adenovirus hepatitis have been reported infrequently.

- Enteric viruses, Virus infections of the enteric system (e.g., coxsackie, echo, and rotaviruses) are most prevalent during the summer and fall months. Infection is usually transmitted by the fecal-oral route. Enteric virus infections among HCT recipients may cause gastroenteritis (coxsackie A, rotavirus, and Norwalk virus) but may also involve other organ systems including the lungs, cardiovascular, and CNS (echovirus).
• Respiratory viruses, infection with RSV, influenza and parainfluenza, and rhinovirus continue to occur during the immediate postengraftment period. Another emerging pathogen in this category is human metapneumovirus.

• Parasitic infections, the occurrence of parasitic infections after HCT frequently requires unique exposures, with the exception of toxoplasmosis.
  - Toxoplasmosis — Reactivation of toxoplasmosis occurs in 5 to 15 percent of T cell depleted or otherwise severely immunosuppressed allogeneic transplant recipients; in other transplant recipients the incidence is less than 1 percent. The infection typically develops in the second month after transplantation, among patients seropositive prior to HCT. Patients with reactivation toxoplasmosis commonly have neurologic deficits and/or seizures, although disseminated disease is also frequent.

• Other, parasitic infections are rare and include strongyloidiasis and cryptosporidiosis. Leishmaniasis and trypanosomiasis can occur in endemic areas.

• Mycobacterial infections, in transplant recipients are rare, occurring in one to three percent of allogeneic and 0.2 percent of autologous HCT recipients. Infection can arise due to reactivation (Mycobacterium tuberculosis and Mycobacterium avium complex) or new exposure (atypical mycobacteria). The most frequent manifestation of tuberculosis is pulmonary infection, which tends to occur during the first three months. Extrapulmonary disease, such as bloodstream, catheter-related, soft tissue, bone and joint infections, is more common with atypical mycobacteria.

**Late Post-Engraftment:** Late infectious complications are typically only seen among allogeneic recipients. The major risk factor for infection during this period is chronic GVHD and its therapy, resulting in:

• Mucocutaneous damage

• Immunodeficiency (eg, cellular and humoral immune dysfunction, hyposplenism, decrease in opsonization, and diminished reticuloendothelial function).

Bacterial infections, late bacteremia is not uncommon after allogeneic HCT and is typically caused by the encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis), staphylococci and gram-negative bacteria, such as Pseudomonas spp. Pneumonia and meningitis are among the complications. The risk of pneumococcal infection is greater among patients with severe chronic GVHD, immunoglobulin deficiency (usually in subclasses IgG2 and IgG4), and hyposplenism. In a review of 47 HCT recipients who developed 54 pneumococcal infections, 50 infections occurred late at a mean of 473 days after transplantation. Bacteremic pneumonia was the most common manifestation, but isolated
pneumonia and bacteremia also occurred. Infection occurred in five patients despite pneumococcal vaccination.

Viral infections, Varicella zoster virus (VZV, the virus that causes chicken pox), EBV, and viruses to which the transplant recipient may have lost immunity figure more prominently as infections during this late postengraftment period.

Varicella zoster virus, the incidence of VZV reactivation is approximately equal among allogeneic and autologous HCT recipients (20 to 40 percent). VZV infection tends to be more common among children (up to 90 percent by year one) and to occur earlier posttransplantation (median 100 days). Infection typically occurs during the first six to nine months (80 percent during first year) and may be associated with complications including:

- Cutaneous dissemination — 25 percent
- Post-herpetic neuralgia — 25 percent
- Scarring — 20 percent
- Bacterial superinfection — 15 percent
- Death — 5 percent
- CNS manifestations — <2 percent

Dissemination following allogeneic HCT appears to be more common than for autologous transplantation HCT (45 versus 25 percent). In addition to skin, dissemination may involve the lungs, liver, and CNS. In HCT recipients, VZV lesions last longer (10 to 14 days) and heal more slowly (3 to 4 weeks) than in normal adults. Immunocompromised patients can also uncommonly develop varicella-like skin lesions with no primary dermatomal eruption; a syndrome termed atypical generalized zoster. Thrombocytopenia and disseminated intravascular coagulation have also been reported. Durable immunity seems to develop following this type of VZV infection, since fewer than five percent of patients have a second episode. Acute GVHD, absolute lymphopenia, and intensive antirejection therapy have been associated with severe and disseminated VZV disease and death.

Epstein-Barr virus, EBV infection in HCT recipients is very common (almost universal in the EBV seronegative recipient who receives a seropositive bone marrow), the incidence of disease is rather low. The median time to onset is between three to five months. The spectrum of EBV infection includes increased oropharyngeal EBV excretion, a non-specific viral syndrome consisting of fever and neutropenia, oral hairy leukoplakia, aplastic anemia, meningoencephalitis, and posttransplant lymphoproliferative disorder (PTLD). PTLD arises from the failure of immune surveillance by EBV-specific T lymphocytes.
resulting in a polyclonal or less often monoclonal B cell proliferation, usually of donor origin. The incidence of PTLD varies from <1 percent of matched related allogeneic HCT recipients to up to 18 percent among high-risk patients. High-risk patients include allogeneic recipients of matched unrelated, mismatched, or T-cell depleted transplants and recipients of high dose antithymocyte globulin or anti-T cell monoclonal antibodies as GVHD prophylaxis. Chronic GVHD is an additional risk factor for PTLD. T cell depletion is the only predisposing factor for PTLD in the autologous transplant setting. Increases in EBV viral load following HCT are common, and are highest in patients at risk for PTLD, suggesting that quantitative viral load surveillance may identify high-risk patients. An infectious mononucleosis-like syndrome may be an early presentation of PTLD. Late manifestations include gastrointestinal tract involvement (25 percent) with risk for bleeding and perforation, and CNS involvement (10 percent). Rarely, PTLD may present as plasmacytoma and circulating paraproteins.

Other viruses, many patients lose their specific B cell immunity to viruses such as measles, mumps, rubella, parvovirus B19, and BK/JC virus, but severe disease with these viruses is rare. Manifestations of these viral infections in HCT recipients can include severe anemia (parvovirus B19), late-onset, prolonged hemorrhagic cystitis, transient hepatic dysfunction, and progressive multifocal leukoencephalopathy (BK/JC virus). BK viruria (reactivation of latent infection) occurs in approximately 50 and less than 10 percent of allogeneic and autologous HCT recipients, respectively.

One case of herpes simplex encephalitis was reported in a patient more than seven months after allogeneic transplantation for chronic myelogenous leukemia. The patient survived, but with neuropsychologic sequelae.

Reactivation of hepatitis B and C viruses after HCT appears to be common (50 to 70 percent), although probably a benign infection. However, primary infection with these viruses is uncommon (2 to 9 percent). The long-term pathology caused by these viruses in patients undergoing HCT remains to be defined.

Infections in Special Situations — while the infections described above apply to all HCT recipients, infection may be more common in some hosts:

- **Asplenia**, Patients who have functional asplenia following HCT or those with previous splenectomy are at risk for infections due to the absence of the spleen.

- **Hypoglobulinemia**, patients with multiple myeloma and chronic lymphocytic leukemia show declining immunoglobulin levels with progression of the disease and especially following allogeneic HCT. Pneumonia, urinary tract, and skin infections caused by encapsulated microorganisms and gram-negative bacilli (eg, Escherichia coli) are most frequent.
• Exposure to purine analogues, patient that have been treated purine analogues such as pentostatin, 2-chloroxyadenosine, and fludarabine has added a new spectrum of infections typically associated with T-cell dysfunction. These include fungal, viral (especially VZV, CMV, HSV), mycobacterial, bacterial (L. monocytogenes), and protozoal (PCP) infections. Listeriosis and PCP may be particularly important if patients are receiving concomitant corticosteroid treatment.

• Environmental risks, HCT recipients can encounter unusual pathogens in the environment related to travel, food and water, or pets.

Quality Of Life after Transplantation:
Quality of Life (QOL) of patients after autologous HCT is generally excellent. The lack of graft vs. host disease in this population and the and the observation from the patient in the first several months after transplant that the underlying disease would be the greatest cause of mortality or morbidity allows the majority on long-term survivors to enjoy a very rewarding QOL. In one study 88% reported a QOL above average or excellent and 78% were employed. Three months after transplantation concerns were expressed regarding employment, appearance, and sexual functioning. At one year these concerns were not reported.

QOL studies on patients receiving allogeneic reported that the majority of patients were employed at one year and in reasonably good health with an acceptable level of subjective and objective function. However, approximately 10-15 percent reported significant evidence of psychosocial stress. Other studies revealed a mild to moderate cognitive dysfunction among patients who received total body irradiation. One study specific to adult allogeneic survivors reported at five years that major limitations were related to physical functioning, including strength, body image and sexual satisfaction.

The largest factors in the allogeneic studies were:

• Age >25 at the time of transplant
• Presence of long-term sequelae
• Presence of chronic graft-versus host disease
• Time from transplant of < 5 years

There have been a number of comparative studies comparing patients who received an autologous transplant vs. an allogeneic transplant, as well as HCT vs. conventional chemotherapy. In the study comparing autologous to allogeneic for patients alive at 12 months the QOL for the patients who underwent allogeneic transplant was much lower. In a study comparing HCT to conventional chemotherapy, the HCT patients reported a good to excellent QOL and in some domains even higher than the chemotherapy patients, but 20% of the HCT patients had lingering problems such as failure to return to work or school, symptoms of anxiety and depression, as well as decreased sexual and body image satisfaction.
Bone Marrow Patient Care Cost Analysis:

Bone-Marrow, Autologous: According to Milliman, the average total cost of an autologous bone marrow transplant or HCT in 2007 was $273,100 in 2007 and $300,400. This figure includes the cost of harvesting the patients bone marrow, at an average of $21,249 in 2007 and $21,200 in 2008; $19,800 in evaluation fees for 2007 and in 2008 this is reported as the cost during the 30 days pre-transplant which is reported as $31,300; in 2007 the physician fees are reported as $21,700 and in 2008 these are reported as $10,600; hospital costs in 2007 were $134,951 and in 2008 they were $169,900; in 2007 post-operative care was reported as $75,400, while in 2008 care is reported as the 180 days post admission fro transplant as $62,100. There are no costs for immunosuppressant medication since the patient is receiving their own cells reported in 2007 while in 2008 Milliman reports all prescriptions post transplant as $5,300.

Bone-Marrow, Allogeneic, Related Match: According to Milliman, the average total cost of an allogeneic, related match transplant or HCT in 2007 was $478,600. This figure includes the cost of harvesting the cells to be infused at an average of $24,223, $20,500 in evaluation fees, $13,700 for doctor's fees, $253,177 in hospital costs, $145,200 in post-operative care and $21,800 for immunosuppressive prescription medications.

Bone-Marrow, Allogeneic, unrelated: According to Milliman, the average total cost of an unrelated allogeneic transplant or HCT in 2007 was $602,200. This figure includes the cost of harvesting the cells at an average of $24,223, $20,500 in evaluation fees, $13,700 for doctor's fees, $354,777 in hospital costs, $167,200 in post-operative care and $21,800 for immunosuppressive prescription medications.

Bone Marrow, Allogeneic, 2008 data total cost is $676,800: Milliman does not differentiate the costs for allogeneic bone marrow transplants by related and unrelated in the 2008 report. The data reported is as follows: 30 days pre-transplant is $30,400; procurement is $29,400; hospital transplant admission is $380,700; physician fees during transplant were $19,600; the 180 days post transplant admission costs were $197,100; and the cost of immunosuppressants and other prescriptions was $19,600.
### AHCCCS Experience with Autologous HCT (based on Data Warehouse numbers eff. 5/09)

<table>
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<th>45 members</th>
<th>Average Encounter Based Allowed Costs for time frame of 2 years pre-transplant</th>
<th>Average Encounter Based Allowed Costs for time frame for 1 year pre-transplant</th>
<th>Average Cost of member during transplant year</th>
<th>Average Cost per member for 1st year post transplant</th>
<th>Average Cost per member for 2nd year post transplant</th>
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AHCCCS Experience with Allogeneic, unrelated HCT (based on Data Warehouse numbers eff. 5/09)

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<th>Average Encounter Based Allowed Costs for time frame of 2 years pre-transplant</th>
<th>Average Encounter Based Allowed Costs for time frame for 1 year pre-transplant</th>
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<th>Average Cost per member for 1st year post transplant</th>
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Insurance Coverage Summary: Medicare covers HCT (http://www.cms.hhs.gov/CertificationandCompliance/20_Transplant.asp#TopofPage); Aetna covers bone marrow transplants based on the condition and then by type of transplant; Medicaid: Kansas covers hematopoietic cell transplants without differentiating between allogeneic related or unrelated; Oregon hematopoietic cell transplants without differentiating between allogeneic related or unrelated with a dollar limit on organ searches; Florida does cover hematopoietic cell transplants for recipients > 21 years; Hawaii covers hematopoietic cell transplants without differentiating between allogeneic related or unrelated

Recommendations: Eliminate unrelated allergenic HCT as the outcomes and mortality demonstrated do not support a risk to benefit analysis. Treatment with chemotherapy, radiation, and surgery when indicated have yielded no better results than an allogeneic, unrelated HCT and in the experience of AHCCCS the results have been worse than national outcomes. Re-evaluate the policy criteria for allergenic, related based on current literature.
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(2) Medicare Coverage criteria

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