

THE RISE OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

Abstract

Hematopoietic stem cell transplantation (HSCT) is a life-saving procedure which is today the standard of care for many hematological malignancies. In recent years its purview has expanded: the procedure has found new utility in the treatment of immunological and hereditary conditions; and other novel areas are being explored as well. Because of this broadening scope of applicability and several recent procedural improvements, insurers need to understand HSCT today. This article provides an overview.

What is HSCT?

Hematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation, is the procedure wherein hematopoietic stem cells (HSC) – that is, blood-forming stem cells – are transplanted with the intention of repopulating the recipient's bone marrow with new, healthy cells. The donor can be the actual patient, a relative, or even an unrelated individual.

The first human allogeneic bone marrow transplant – transplantation from an outside donor – was performed in 1957 by physician and cancer researcher Dr. E. Donnall Thomas, who is also known as the father of bone marrow transplantation. Initial results were disappointing, with very high mortality due to graft failure, graft vs. host disease (GVHD), and primary disease relapse.

The procedure did, however, establish that bone marrow infusion could lead to hematological reconstitution in patients with acute leukemia.¹ Major progress came in the late 1960s with the discovery of the human leukocyte antigen (HLA) system by immunologists Dr. Jean Dausset, Dr. Johannes Joseph Van Rood, and Rose O. Payne, Ph.D. The HLA is what enables the human immune system to distinguish its own proteins from those of foreign entities.^{2,3} Its discovery permitted unrelated donors to be typed and matched to recipients, which increased the success rate of these transplants. In 1980, Dr. Dausset received the Nobel Prize in Physiology or Medicine, together with Baruj Benacerraf and George Davis Snell, for their discoveries of “genetically determined structures on the cell surface that regulate immunological reactions.” Dr. Dausset was recognized for his identification of human leukocyte antigens and the genes that code for them. In 1990, Dr. Thomas received a Nobel Prize in Physiology or Medicine as well for his work in cell transplantation.

Today, HSCT is standard of care for many hematological malignancies, and hematopoietic stem cells are the most routinely transplanted type of adult stem cell. More than one million HSCTs have reportedly been performed worldwide during the past six decades; this number is steadily rising,⁶ and survival rates are improving.

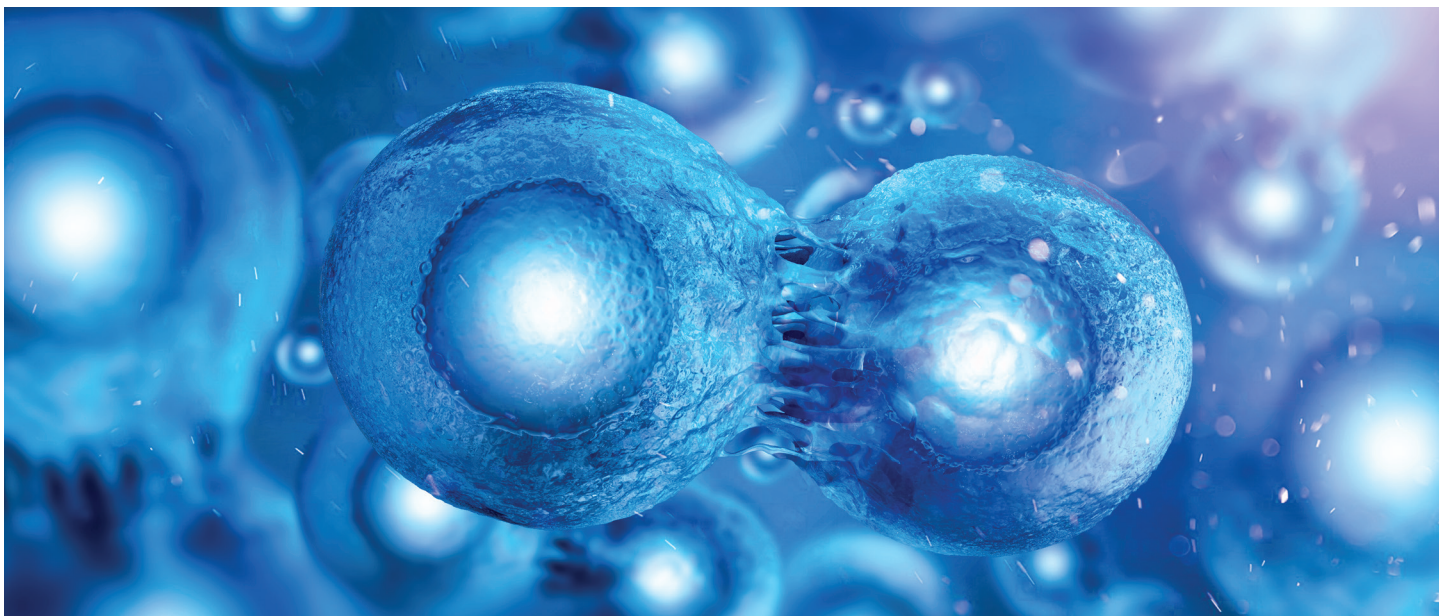
ABOUT THE AUTHOR



Dr. Sheetal Salgaonkar, DBIM
ssalgaonkar@rgare.com

Dr. Sheetal Salgaonkar, DBIM, is Vice President and Medical Director with RGA and a member of RGA's Global Medical team. Based in Mumbai, India, she provides underwriting and claims consultation for the regional offices in the International division, and is involved in product development, medical underwriting training, and development of guidelines for RGA's Global Underwriting Manual.

Dr. Salgaonkar has been a part of the Federation of Indian Chambers of Commerce & Industry's Task Force for Critical Illness and a member of the subcommittee for Policy Formulation on Financial Inclusion of Persons with Disabilities for the Indian Insurance Industry. She is also treasurer of the Indian Insurance Medical Officer's Association (IMOK) and was the scientific chair for the International Committee for Insurance Medicine's 2019 meeting, held in Mumbai. She has significantly contributed to the course curriculum of the Underwriting Diploma and Advanced Underwriting Diploma, which is a joint initiative of Association of Insurance Underwriters (AIU) and Insurance Institute of India.



About Stem Cells

Stem cells are nonspecialized (or basic or generic) cells of multicellular organisms. All stem cells have two fundamental characteristics: the ability to duplicate precisely by cell division, known as self-renewal, so that the daughter cells are exactly the same as the parent cells; and differentiation, which refers to the ability of these cells to mature into a wide range of specialized cells.

There are three main types of stem cells:

- Totipotent, also called omnipotent, which are stem cells with the potential to become any cell of an organism, including the umbilical cord and placenta. The zygote is an example of a totipotent stem cell.
- Pluripotent, also known as embryonic stem cells, which can differentiate into every type of cell in an organism except the umbilical cord and placenta. These cells are descendants of totipotent cells.
- Multipotent, also known as adult stem cells or somatic stem cells, which are found throughout an organism after cell differentiation and development. Multipotent cells can differentiate into a number of cell types, but only those in closely related cell families. Hematopoietic, neural, and mesenchymal cells are types of multipotent stem cells.

Types of HSCTs

The two types of HSCT procedures utilized today are autologous, where the donor and the patient are the same, and allogeneic, where the donor is other than the patient.

The advantages of autologous transplantation include faster patient cell count recovery, less transplant-related morbidity, shorter hospital stays, and reduced cost compared with allogeneic grafts. Relapse of the underlying malignancy is the major risk.⁵

Allogeneic transplants consist of hematopoietic stem cells from an external donor. An advantage of an allogeneic graft is that the donor's immune system can contribute significantly to the elimination of cancer via graft vs. tumor (GVT) effect.⁶ The risk of disease relapse is low, but the procedure is associated with graft vs. host disease (GVHD).

Indications

Indications for HSCT are constantly being expanded and refined, as research progresses and new efficacies are discovered (Table 1, below). The American Society for Blood and Marrow Transplantation (ASBMT) and the European Blood and Marrow Transplantation Group (EBMT) have published guidelines that classify the many conditions for which HSCT is an indicated treatment. The guidelines provide three categories of indications: standard of care, including clinical option; developmental; and not generally recommended.

The majority of HSCTs performed for lymphoid malignancies, are autologous, while most done for myeloid malignancies are allogeneic. Autologous HSCT is also preferred for patients with autoimmune disorders.^{7, 8, 9}

Table 1: Indications for HSCT

Category	Indications
Hematologic malignancies	64% lymphoid malignancies • Acute lymphocytic leukemia (ALL) • Chronic lymphocytic leukemia (CLL) • Hodgkin lymphoma (HL) • Non-Hodgkin lymphoma (NHL) • Plasma cell disorders (PCD), including multiple myeloma (MM) and others
	25% myeloid malignancies • Acute myeloid leukemia (AML) • Myelodysplastic or myelodysplastic/myeloproliferative neoplasm (MDS or MD/MPN overlap) • Myeloproliferative neoplasm (MPN) • Chronic myeloid leukemia (CML)
Solid tumors	4% solid tumors • Pediatric solid tumors • Soft tissue tumors • Breast cancer • Renal cancer
Nonmalignant disorders	7% nonmalignant disorders • Hemoglobinopathies (sickle cell disease, thalassemia) • Inherited metabolic disorders • Bone marrow failure • Primary immunodeficiencies • Autoimmune disorders (multiple sclerosis, systemic sclerosis)

HSCT For All – A Closer Reality

The availability of various sources of stem cells as well as alternative donor options have made it possible to offer HSCT as a treatment option for a wider group of patients.

Hematopoietic stem cells can come from three sources: harvested bone marrow, peripheral blood stem cells, and umbilical cord blood.⁷

Bone marrow cells are harvested from donors in a surgical procedure. They are extracted either from the hip bone (specifically, the posterior iliac crest) or from the sternum. Since the 1990s, scientists have been able to collect stem cells directly from peripheral blood. The procedure involves an injection of granulocyte colony stimulating factor (G-CSF), which causes marrow stem cells to migrate into circulating blood. Peripheral blood stem cells (PBSCs) can then be collected by apheresis, which is a much less invasive procedure than bone marrow collection. Over the past decade, PBSCs have become the preferable stem cell source for many transplant centers, accounting for around 75% of all HSCTs.¹⁰



PBSC patients benefit from faster engraftment, but the risk is higher rates of GVHD.¹⁰ High-level evidence has shown that there is no difference in overall and disease-free survival between bone marrow and PBSC HSCTs.¹¹

Umbilical cord blood (UCB) cells are an alternative source to bone marrow cells and PBSCs. These cells, as the name implies, are extracted from the umbilical cord after birth. UCB offers several advantages: easier availability, higher tolerable HLA disparity as the cells are naive, and lower risk of GVHD and relapse.

HLA Matching

The strongest determinant of outcomes for allogeneic HSCT is donor-recipient human leukocyte antigen (HLA) matching.¹² HLA matching identifies the HLA A, B, C (Class I) and DR, DQ, DP (Class II) loci present on donor and recipient cells. Each person has two types of A, B, C, and DR antigens, one inherited from each parent.

The best donor for an allogeneic HSCT is either an HLA-matched sibling or an unrelated donor who is a complete HLA match (8/8 or 10/10). Unfortunately, less than 30% of patients have a sibling who is a complete match.¹³ If an adult-matched sibling or matched unrelated donor (MURD) cannot be identified, recent advances in HLA research have enabled three alternative donor options:

- **Mismatched unrelated donor (MMURD).** This refers to an adult unrelated donor who is mismatched in at least one antigen or allele at HLA-A, B, C, or DR.
- **Haploidentical-related donor.** This would be a family member with only one of the two HLA haplotypes genetically identical with the patient. These are usually biological parents, children, or siblings.
- **Umbilical cord blood (UCB) stem cells.** UCB stem cells from unrelated donors are commonly used when a donor match is otherwise unavailable. Since these cells can be obtained rapidly from cord blood banks, they may be a better option when the patient need is urgent. The downside is that cord blood contains fewer hematopoietic stem cells than bone marrow or peripheral blood, so engraftment tends to be slower, the risk of graft failure is higher, and immune reconstitution can be slower, which may lead to infections.¹⁴

An exciting new development is the use of either autologous or unrelated UCB cells in therapies for diseases such as cerebral palsy, hypoxic ischemic encephalopathy, and dilated cardiomyopathy.¹⁵



The Procedure

HSCT generally requires four steps, depending on the source of the stem cells:

- **Cell collection.** HSCs are collected either by apheresis from peripheral blood or by bone marrow harvest. PBSCs are collected after stimulation either with growth factors alone or growth factors plus chemotherapy.
- **Processing and cryopreserving.** HSCs are then processed and cryopreserved until needed for transplant.
- **Preparation and conditioning.** These regimens aim to eradicate diseased cells, suppress the recipient's immune system, and create space for donor cells in the recipient's marrow. Traditionally, myeloablative regimens (MA), which used high doses of chemotherapy and total body irradiation (TBI), were used for preparation and conditioning. A major development over the past 15 years has been the development of reduced intensity conditioning (RIC) and nonmyeloablative (NMA) conditioning. These regimens keep treatment intensity just high enough to avoid graft rejection. The goal is to promote engraftment and let the GVT effect eliminate tumor cells. The reduction in morbidity and mortality in transplants where RIC and NMA regimens were used has made allogeneic HSCT available for patients age 60 and older – the age group with the highest prevalence of most hematopoietic malignancies.¹⁶ (Table 2, below)
- **Stem cell infusion.** After conditioning, the stem cells are infused intravenously.

Table 2: Conditioning regimens – favorable and unfavorable factors

Myeloablative	Nonmyeloablative or Reduced Intensity
• Used in patients who are younger and with no comorbidities	• Can be used in older patients with comorbidities
• Dose-intensive chemotherapy +/- TBI	• Lower doses of chemotherapy + /- TBI
• Eradicates malignant disease	• Reduces conditioning-related toxicity
• Suppresses immune system to prevent graft rejection	• Relies mainly on GVT effect

Complications

Although outcomes of HSCT tend to be good and patients show considerable improvement over time, the procedure is associated with significant related morbidity, mortality, and long-term health issues.

Major complications include:

- **Infections** are the most important cause of morbidity and mortality during the post-transplant period of neutropenia. In the pre-engraftment period (0-30 days after transplantation) bacterial infections followed by fungal infections (e.g., *Candida*, *Aspergillus*) predominate due to low white blood cell counts and the disruption of normal barrier defenses.¹⁷ The most important pathogens in the early post-engraftment period (30 to 100 days) are viruses such as cytomegalovirus (CMV) and other pathogens such as *Pneumocystis* and the previously mentioned *Aspergillus*. In later stages (>100 days post transplantation), the immune system recovers, reducing the risk of opportunistic infections. Chronic GVHD (discussed in the next section) and continued immunosuppression can lead to infection with viruses such as CMV, varicella zoster virus (VZV or shingles), and Epstein-Barr virus (EBV), as well as with encapsulated bacteria such as *Hemophilus influenzae* and *Streptococcus pneumoniae*.^{18,19}

- **Graft vs. Host Disease (GVHD)**, which is the major complication of allogeneic HSCT, is an immunologically mediated reaction of donor cells (the graft) to host (or recipient) cells. GVHD develops in >50% of these patients despite prophylaxis and can be life-threatening.

For GVHD prophylaxis, patients receive immunosuppressive drugs, most commonly a combination of cyclosporine and methotrexate or mycophenolic acid. In contrast to organ transplantation, GVHD prophylaxis can be tapered off and stopped in patients who do not develop GVHD after six to 12 months.²⁰

GVHD can be acute or chronic. Although GVHD has traditionally been classified as acute or chronic based on a cutoff of 100 days after transplantation, it is now widely recognized that there is extensive overlap in the time course at presentation. Each is a clinically distinct entity with very different pathophysiologic mechanisms.

- **Acute GVHD** generally develops within the first four to five weeks after transplant. Its incidence and severity are directly related to the degree of HLA mismatch. It is an inflammatory reaction involving the skin, the liver, and the GI tract.²¹
- **Chronic GVHD (cGVHD)** resembles an autoimmune disorder. Fibrosis and sclerosis of involved tissues are its characteristic features. In severely affected individuals it can involve multiple organ systems, including skin, musculoskeletal, gastrointestinal, lungs, GI, eyes, liver, and genitourinary systems. cGVHD is a major cause of long-term morbidity and mortality in survivors of HSCT and is the most significant determinant of post-transplant quality of life as well. Risk factors for cGVHD include older age, prior acute GVHD, donor type, and use of PBSCs.^{22, 23}
- **Graft failure/rejection** is an uncommon but serious complication of HSCT. It is defined as either lack of initial engraftment of donor cells (primary graft failure) or loss of donor cells after initial engraftment (secondary graft failure). Risk factors include RIC/NMA regimens, UCB transplants, and HLA-mismatched transplants.²⁴

- **Secondary malignancies** are a post-HSCT concern. The magnitude of risk of secondary malignancies shows a 4- to 11-fold relative risk (RR) in several studies and a cumulative incidence at 15 years of 10% to 12%.²⁵ Secondary malignancies are divided into three groups:

- **Post-transplant lymphoproliferative disorders (PTLD)**, which are almost exclusively seen in allogeneic HCT recipients and comprise a heterogeneous group of lymphoid proliferations primarily involving B-lymphocytes, which result from EBV infection.
- **Hematologic malignancies**, such as MDS and AML.
- **Solid cancers**, with lifelong cancer screening recommended for all HCT survivors in accordance with established guidelines.

Post-Transplant Prognosis and Survival

HSCT outcomes are influenced by the patient's age, the nature and stage (if cancer) of the disease, and transplant-specific variables such as donor/recipient histocompatibility and the time interval from diagnosis to transplant.

Disease relapse is the main cause of treatment failure in the first two to four years after transplantation. Patients who do not relapse through this time period have relatively high rates of subsequent survival.

Cumulative chemotherapy and radiation exposures can injure normal tissues, leading to premature onset of chronic health conditions such as subsequent neoplasms, congestive heart failure, coronary artery disease, and endocrine and musculoskeletal abnormalities.

Pediatric HSCT survivors are more likely to experience psychological distress and low quality of life in adulthood compared with the general population.²⁶

Long-term HSCT survivors need continued lifelong surveillance for screening, early detection, and timely treatment of late complications. Although studies vary in methodology and patient characteristics, together they indicate high probability of long-term survival in this patient population, although their life expectancy continues to lag that of age- and gender-matched peers from the general population for at least 15 to 20 years after HSCT.²⁷



Applications of HSCT in Insurance

From an underwriting point of view, HSCT is a curative therapy for many malignant and nonmalignant hematological diseases. Although the primary disease is a major factor, individuals who have undergone HSCT still have long-term effects and might be offered life cover with a mild-to-moderate risk assessment a few years after a complication-free time interval has passed. HSCT survivors may have morbidity issues such as treatment-related chronic conditions as well as psychological distress and low quality of life. Therefore, offering living benefits may not be feasible.

HSCT is covered as a major payout in many critical illness products. Definitions vary, and a few points raise concern:

- Some policy definitions cover only HSCT recipients who have undergone MA conditioning regimes. With the increasing use of RIC/NMA regimens for the same primary disease, definitions need to be updated and priced accordingly, as such claims could arguably otherwise meet the definition.

- Most policy definition wordings exclude stem cell transplants, but as HSCT is a type of stem cell transplant, a rewording of the definition would be technically appropriate.
- Some products cover only allogeneic transplants, the view being that autologous HSCT uses a patient's own cells and so are not equivalent. However, as autologous and allogeneic transplants are performed for the same hematological indications, employ nearly identical procedures, and have the same potential complications, this view can be challenged.

Conclusion

HSCT is a curative treatment for many hematological malignancies as well as immunological and hereditary conditions. Over the years, several advances, such as new conditioning regimes (NMA and RIC) and alternative donor and cell source options, have made HSCT safer, leading to increasing numbers, expanding indications, and improved patient survival. In the coming years, HSCT is likely to become more common, efficient, and effective. 

References

1. Thomas ED, et al. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *New Engl J Med*. 1957 Sep 12; 257: 491-6. https://www.nejm.org/doi/full/10.1056/NEJM195709122571102?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
2. Dausset J. Iso-leuko-antibodies. *Acta Haematol*. 1958 Jul-Oct; 20(1-4): 156-66. <https://www.ncbi.nlm.nih.gov/pubmed/13582558>
3. Van Rood JJ. The detection of transplantation antigens in leukocytes. *Semin Hematol* 1968 Apr; 5(2): 187-214. <https://www.ncbi.nlm.nih.gov/pubmed/4871670>
4. Niederwieser D, et al. One and Half Million Hematopoietic Stem Cell Transplants (HSCT). Dissemination, Trends and Potential to Improve Activity By Telemedicine from the Worldwide Network for Blood and Marrow Transplantation (WBMT). *Blood*. 2019 Nov 13; 134(suppl 1): 2035. https://ashpublications.org/blood/article/134/Supplement_1/2035/427903/One-and-Half-Million-Hematopoietic-Stem-Cell
5. Saba N, Abraham R, Keating A. Overview of autologous stem cell transplantation. *Crit Rev Oncol Hematol*. 2000 Oct; 36(1): 27-48. <https://www.ncbi.nlm.nih.gov/pubmed/10996521>
6. Horowitz MM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood*. 1990 Feb 1; 75(3): 555-62. <https://www.ncbi.nlm.nih.gov/pubmed/2297567>
7. Sureda A, et al. Indications for allo- and auto-SCT for haematological diseases, solid tumors and immune disorders: current practice in Europe, 2015. *Bone Marrow Transplant*. 2015 Aug; 50(8): 1037-56. <https://www.ncbi.nlm.nih.gov/pubmed/25798672>
8. Passweg JR, et al. The EBMT activity survey report 2017: a focus on allogeneic HCT for nonmalignant indications and on the use of non-HCT cell therapies. *Bone Marrow Transplantation*. 2019 Oct; 54(10): 1575-85. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6957459/>
9. Majhail NS, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015 Nov; 21(11): 1863-9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4830270/>

10. Körbling M, Freireich EJ. Twenty-five years of peripheral blood stem cell transplantation. *Blood*. 2011; 117(24): 6411-6. <https://ashpublications.org/blood/article/117/24/6411/22173/Twenty-five-years-of-peripheral-blood-stem-cell>
11. Gratwohl A, et al. Quantitative and qualitative differences in use and trends of hematopoietic stem cell transplantation: A Global Observational Study. *Haematologica*. 2013 Aug; 98(8): 1282-90. <https://www.ncbi.nlm.nih.gov/pubmed/23508009>
12. Petersdorf EW. The major histocompatibility complex: a model for understanding graft-versus-host disease. *Blood*. 2013 Sep 12; 122(11): 1863-72. <https://ashpublications.org/blood/article/122/11/1863/31868/The-major-histocompatibility-complex-a-model-for>
13. Ballen KK, et al. The national marrow donor program 20 years of unrelated donor hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2008 Sep; 14(9 Suppl): 2-7. <https://www.ncbi.nlm.nih.gov/pubmed/18721774>
14. Kekre N, Antin JH. Hematopoietic stem cell transplantation donor sources in the 21st century: choosing the ideal donor when a perfect match does not exist [correction in *Blood*. 2015 Feb 5; 125(6):1048]. *Blood*. 2014 Jul 17; 124(3): 334-43. <https://www.ncbi.nlm.nih.gov/pubmed/24914138>
15. Ballen K. Umbilical Cord Blood Transplantation: Challenges and Future Directions. *Stem Cells Translational Medicine*. 2017 Apr 29. 6(5): 1312-5. <https://stemcells.journals.onlinelibrary.wiley.com/doi/full/10.1002/sctm.17-0069>
16. Gyurkocza B, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. *J Clin Oncol*. 2010 Jun 10; 28(17): 2859-67. <https://www.ncbi.nlm.nih.gov/pubmed/20439626>
17. Leather HL, Wingard JR. Infections following hematopoietic stem cell transplantation. *Infect Dis Clin North Am*. 2001 Jun; 15(2): 483-520. <https://www.ncbi.nlm.nih.gov/pubmed/11447707>
18. Sahin U, et al. An overview of infectious complications after allogeneic hematopoietic stem cell transplantation. *J Infect Chemother*. 2016 Aug; 22(8): 505-14. <https://www.ncbi.nlm.nih.gov/pubmed/27344206>
19. Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. *Clinical Infectious Diseases*. 2001 Jul 15; 33(2): 139-44. <https://academic.oup.com/cid/article/33/2/139/323987>
20. Ruutu T, et al. Prophylaxis and treatment of GVHD after allogeneic haematopoietic SCT: a survey of centre strategies by the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2012 Nov; 47(11): 1459-64. <https://www.ncbi.nlm.nih.gov/pubmed/22410750>
21. Jagasia M, Arora M, Flowers ME, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood*. 2012 Jan 5; 119(1): 296-307. <https://www.ncbi.nlm.nih.gov/pubmed/22010102>
22. Cooke KR, et al. The Biology of Chronic Graft-versus-Host Disease: A Task Force Report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*. 2017 Feb; 23(2): 211-34. <https://www.ncbi.nlm.nih.gov/pubmed/27713092>
23. Arora M, et al. Chronic GVHD Risk Score: a Center for International Blood and Marrow Transplant Research Analysis. *Blood*. 2011 Dec 11; 117(24): 6714-20. <https://www.ncbi.nlm.nih.gov/pubmed/21493797>
24. Olsson R, et al. Graft failure in the modern era of allogeneic hematopoietic SCT. *Bone Marrow Transplantation*. 2012 Dec 10; 48: 537-43. <https://www.nature.com/articles/bmt2012239>
25. Ortega JJ, et al. Secondary malignancies and quality of life after stem cell transplantation. *Bone Marrow Transplantation*. 2005 Apr 6; 35: S83-7. <https://www.nature.com/articles/1704854>
26. Sinatoro F, et al. Quality of Life and Psychopathology in Adults Who Underwent Hematopoietic Stem Cell Transplantation (HSCT) in Childhood: A Qualitative and Quantitative Analysis. *Front Psychol*. 2017 Aug 8; 8: 1316. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5550669/>
27. Wingard JR, et al. Long-Term Survival and Late Deaths After Allogeneic Hematopoietic Cell Transplantation. *Journal of Clinical Oncology*. 2011 Jun 1; 29(16): 2230-9. <https://ascopubs.org/doi/10.1200/JCO.2010.33.7212>