International Journal of Applied Chemical and Biological Sciences (2022), 3(1), 31-44
ISSN 2582-788X

REVIEW PAPER

Article Identifier: https://identifier.visnav.in/1.0001/ijacbs-21l-19006/

# Physiological changes in a patient undergoing Bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation

Bhadra, A. *

Department of Biotechnology, School of Bioengineering and Biosciences, Lovely Professional University, India

* For correspondence: anumita1996@gmail.com

*Received on: 19 December 2021* *Published on: 13 January 2022*

**ABSTRACT**

Stem cell transplantation has been used for treating numerous diseases since the time its potentiality was identified. Doctors employ this technique to treat many types of blood cancers that damage or destroy the bone marrow. It is also used to restore bone marrow that has been damaged during cancer treatments such as radiation or chemotherapy. A stem cell transplant puts healthy blood stem cells back into the patient's body so that they can produce healthy blood cells and get the immune system working again. When the healthy stem cells come from a donor, it's called an allogeneic hematopoietic transplant. But such treatments have a high risk of infections associated. After the transplantation, patients are prone to various physiological changes for at least a few weeks before their bodies re-start producing blood cells on their own. It is always better to be aware of the various infections that a patient may suffer and the physiological changes faced by them before and post the transplantation. This article gives an insight into the various complications concerning patients with allogeneic hematopoietic stem cell transplantation with a detailed view of the causes of the reasons to go for such transplant and survival post such infection. Biomarkers have been found highly beneficial in the timely prediction of the onset of such allogeneic transplantation-induced diseases.

*Keywords* - stem cell transplantation, bone marrow, allogeneic hematopoietic transplant, biomarkers

## 1. INTRODUCTION

Hematopoietic stem cell transplant (HSCT) is a replacement of recipient bone marrow with donor hematopoietic stem cells obtained either from autologous (self), or allogeneic (donor). HSCs can be obtained either from peripheral blood or from bone marrow/cord blood (in the case of an umbilical cord blood transplant). In the 1900s, this technique was hugely adopted and practiced with increasing frequency while treating numerous malignant and nonmalignant diseases [1].

Hematopoietic stem cell transplantation (HSCT) involves the intravenous infusion of hematopoietic stem cells to re-establish blood cell production in patients whose bone marrow or immune system is damaged or defective. Firstly, an indication for transplant must be present. Next, a potential donor is identified, usually a

sibling or unrelated donor. This is followed by typing of the patient and donor for human leukocyte antigens, or HLA is done and potential matches are identified and the best donor is selected [2]. A work-up on the patient and donor is done. Once the patient is admitted for the transplant, the patient goes to a conditioning phase immediately before the infusion of the hematopoietic stem cells. Immunosuppressant is started before and after the infusion and continued for 6 months. It may even last for a year after the bone marrow transplant. As the only therapeutic method, allogenic hematopoietic stem cell transplantation (HSCT) has been widely applied for the treatment of various hematological malignancies- e.g., acute leukemias, chronic myeloid leukemias, relapse lymphomas, and sometimes refractory relapsed myeloma. Some common non-malignant stem cell diseases for which allogeneic stem cell transplantation is done are the bone marrow failure syndromes like aplastic anemia, immunodeficiency diseases, and genetic diseases. Allogenic hematopoietic stem cells can be obtained from a related donor, usually a sibling or less commonly a haploidentical donor and this may be a parent or child of a patient or even a sibling with a half match HLA [3]. An unrelated donor is usually an adult or in the case of a cord blood transplant where the source is cord blood.

For HLA matching, doctors look for donor cells that are histocompatibility with that of the recipient at HLA-A, HLA-B, HLA-DRB1, and HLA-C loci. The patient is then evaluated by the transplant physician and primary physician for suitability to proceed with the transplant. Screening of the recipient of the patient is done to evaluate the organ function. Donor screening is done to make sure that it is safe for the donor to undergo the procedure of stem cell harvesting and whether it is safe for the recipient to receive the cell product from the particular donor.

Before the infusion of the stem cells, the patient will undergo a conditioning phase. The process involves the administration of chemotherapy, radiotherapy, and/or immunotherapy in varying combinations. The purpose of this process is to eradicate residual diseases like leukemic cells, and suppression of host immune system so that the patient can readily accept the graft, and also for the creation of cells for donor cells in the recipient's bone marrow. The conditioning regimens used can be broadly divided into myeloablative conditioning, reduced-intensity conditioning, or nonmyeloablative conditioning [4].

Myeloablative conditioning involves dose-intensive chemotherapy with or without total body radiation, and the goal is to irradicate disease, in addition to suppressing the recipient's immune system to prevent graft rejection. The reduced intensity of a non-myeloablative conditioning regimen involves the use of lower doses of chemotherapy and total body radiation. The aim of this is to reduce the toxicity related to the conditioning chemotherapy itself. These rely mainly on the graft-versus-tumor effect to fight residual disease [5]. The hematopoietic stem cells are infused into the patient as are for other blood products under monitoring. Engraftment, which is when the donor cells start to grow and blood counts recover, depends on the source of the stem cells. Immunosuppressive agents are stopped just before the infusion of stem cells and continued usually for approximately 6 months to a year or maybe longer, depending on the presence of chronic graft versus host disease.

Many complications can arise as a result of a bone marrow transplant. During infusion, anaphylactic reactions or hemolysis with renal impairment can occur. Potentially fatal infections can also occur when a patient's WBCs count drops after immunotherapy or before lymphocyte function recovers. Drug toxicities can occur as well as graft versus host disease. In the long

term, chronic graft versus host disease and secondary malignancies are potential complications.

## 2. EPIDEMIOLOGY

Having an understanding of the epidemiology of infections & diseases post allogeneic hematopoietic stem cell transplantation (HCT) is extremely important and essential to carry out numerous preventive measures and to efficiently diagnose and treat individual patients. With the advancement made in the field of antiretroviral therapy (HAART) back in 1996, there has been a steep decline in the rate of disease in the population and death rate among patients suffering from human immunodeficiency virus (HIV) infection [6].

More patients undergoing treatment through HAART will be able to maintain a very low viral load and will not become positive for AIDS [7]. Not adhering to the highest standards and quality, the medicines taken by patients lead to high chances of mutational selection which confers resistance to the antiretroviral therapy and then to virologic failure. Such conditions pose a huge challenge despite the less complicated technique of HAART, primarily with fewer adverse effects and pill burden. While the probability of occurrence of HIV remains stable, its incidence has been on a surge especially during the previous decade due to a fall in the death rate [8].

Studies using the computational model approach have predicted that it would take approximately about a period of 70 years of suppression of the viral activity causing it for a person infected by that virus to achieve a virologic cure of HIV [9]. While there are some reports of case studies from Germany showing an HIV-infected person being cured of the infection post-treatment rendered by allogeneic hematopoietic stem cell transplantation (HSCT) [10]. The transplantation was successfully achieved by inserting a CCR5Δ32 homozygous donor for acute myeloid leukemia into the patient. Such transplantation therapy had caught the eyes of researchers and doctors equally and as a result, extensive scientific inquiry was initiated for understanding the potential role of HSCT in successfully curing HIV. Another study was conducted on two patients who were positive for HIV in Boston to check the credibility of allogeneic. It was concluded that the patients sustained a temporary diminution of HIV for 12-32 weeks after pausing the antiretroviral therapy (HAART). However, the patients had persistent, detectable levels of HIV in the blood after a certain phase of undetectable levels [11].

It was observed in another recent study that patients with HIV infection are safe for undergoing autologous HSCT for HIV-related lymphoma [12]. There has been great progress in HIV-associated cancers' clinical trials that are ongoing to study the conclusion of HSCT, yet the results for the same are limited, especially in allogeneic HSCT [13]. While it was initially noted, the outcomes were similar for both HIV-positive as well as HIV-negative patients who underwent HSCT [14-15]. However, the studies are limited by small sample size or lack of recent data [16].

In recent times, there has been a surge in clinical diagnostic options because of advances made in genetic engineering. With this advancement made in diagnosis, spotting a primary immunodeficiency disease (PID) has been possible and their causes (refractory autoimmunity, cytopenias, immune dysregulation, and hematologic malignancy) were identified [17-18]. The adult population is affected mostly by PID. Many grown-up people suffering from PID can enjoy the advantage of allogeneic hematopoietic stem cell transplantation [19]. There is an international expert committee that provides details of such patients every year who suffer from genotypic and phenotypic inborn errors of immunity.

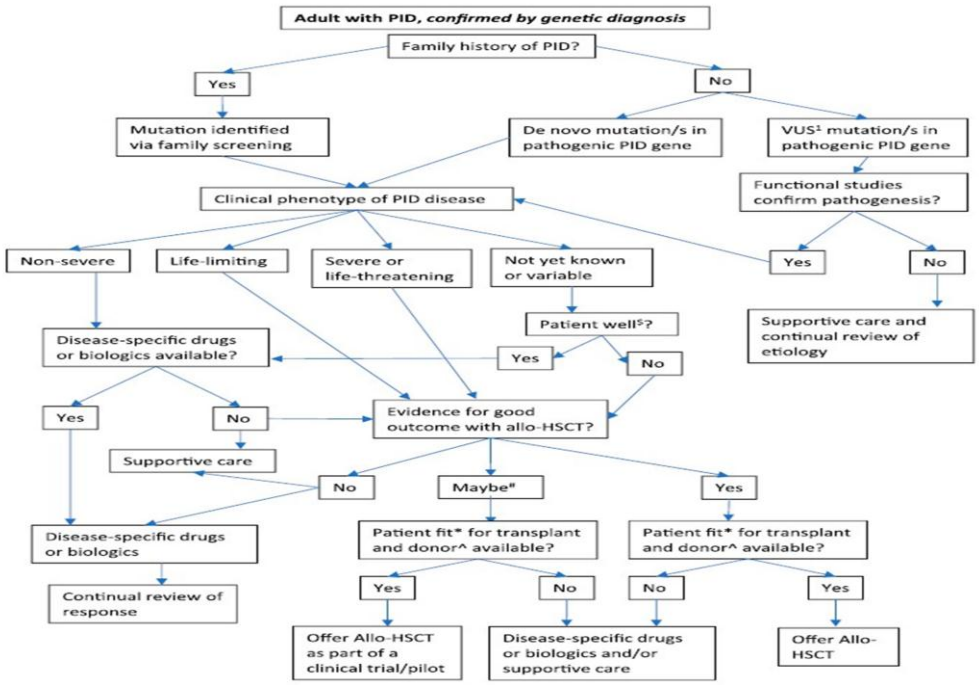


**Figure 1.** Adult PID patients with a genetic diagnosis referred for allogeneic HSCT [17]

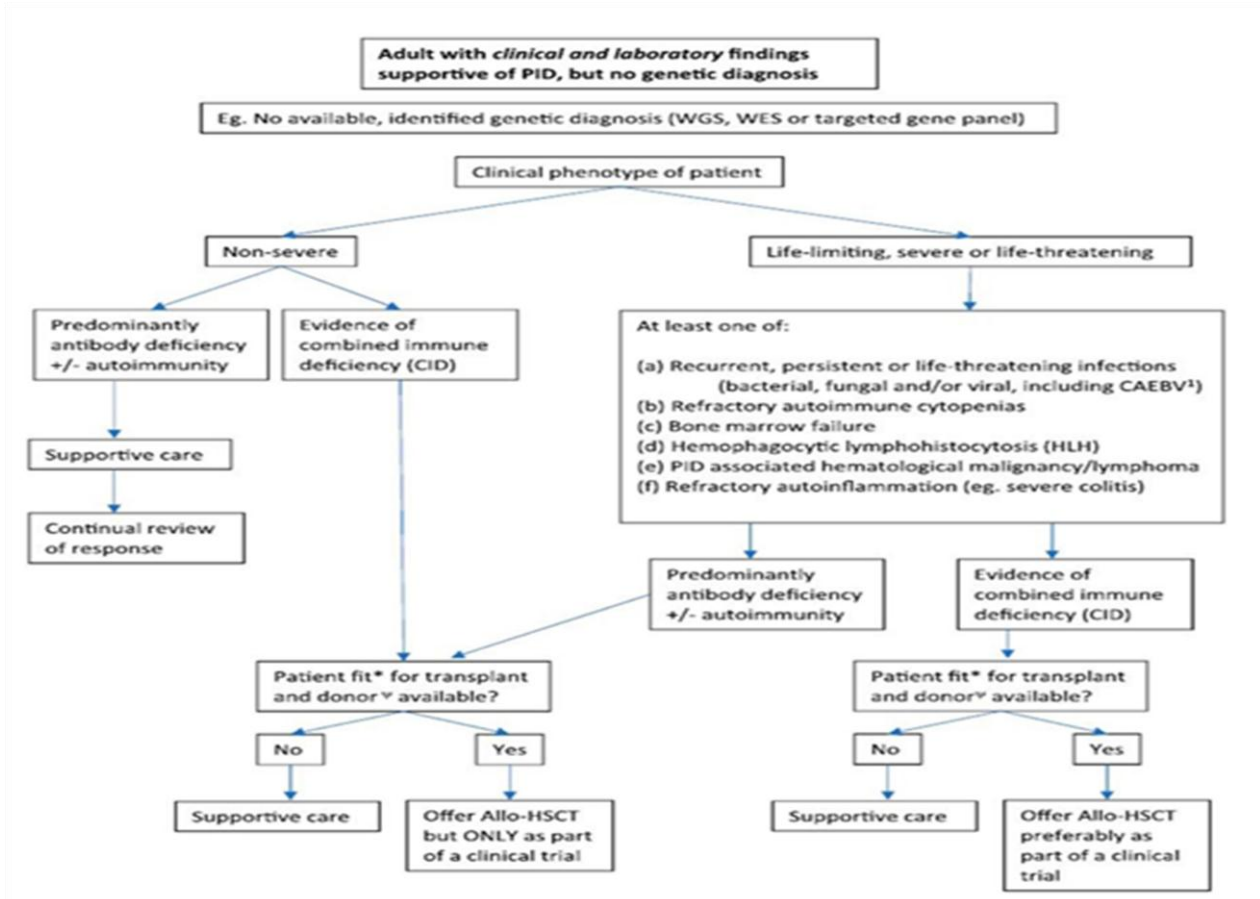


**Figure 2**. Adult PID patients with genetic diagnosis referred for allogeneic HSCT [17]

Statistics show about 406 distinct clinical disorders with 430 different gene defects [19]. Although such individuals suffering from these genetic disorders are extremely rare, they are especially found in individuals

with hematologic malignancies and autoimmune cytopenias. Today, such diseases have been framed under new classifications and are termed as autoimmune, autoinflammatory conditions, or syndromal disorders concerning immunodeficiency. Several such gene defects could be cured by allo-HSCT therapy, but in some cases of syndromal disorders, only a portion of the defect which is hematopoietic in nature can be rectified. Usually, medical practitioners proceed with HSCT for adults with PID, based on their clinical diagnosis alone, but it is equally important to know the family history of the patient for a precise genetic diagnosis. The doctor should also be aware of the patient's published transplant experience and any other extra information in connection hematopoietic perspective of the disease. Then allogeneic hemopoietic stem cell transplantation would be highly beneficial for the patient.

Another such genetic disease that requires allo-hematopoietic stem cell transplant is Severe combined immunodeficiency (SCID). The enzyme, ADA deaminates adenosine or deoxyadenosine make inosine or deoxyadenosine, which can then either be excreted ultimately as uric acid or salvaged. It is seen that in the absence of ADA genetic deficiency when ADA enzymes were missing in a SCID patient, it led to the suggestion that it could be involved in the disease. Conclusions have been reached that in absence of ADA, high levels of the nucleoside that build up are phosphorylated, especially in lymphocytes to deoxyadenosine triphosphate and this lymphotoxin kills off the immune system and leads to ADA SCID [20].

ADA SCID is about 10-15% of all human SCID and is estimated that there are about 10 children a year in U.S. and Canada only born with it. There are different forms of SCID, the first one where the human's biochemical and genetic basis were determined as reasons causing them. ADA deficient SCID patients have profound pan-lymphopenia, i.e., they have low levels of T-B-NK lymphocytes from these accumulated lymphotoxin adenine metabolites [21].

It can be donor or from a haploidentical, usually a parent donor [22]. Bone marrow is used as a source of hematopoietic stem cells. These are harvested from the patient to the operating room, taken to the GMP laboratory where researchers are enriched for the CD34

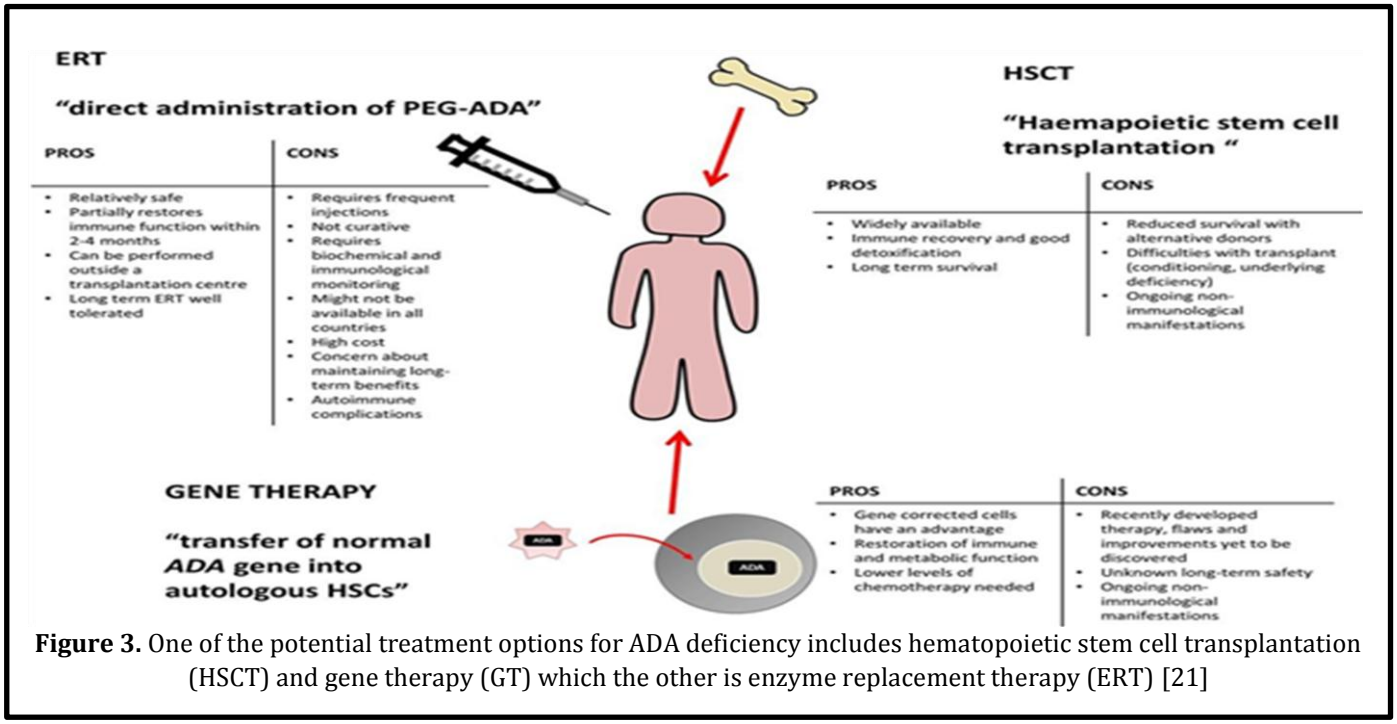


**Figure 3.** One of the potential treatment options for ADA deficiency includes hematopoietic stem cell transplantation (HSCT) and gene therapy (GT) which the other is enzyme replacement therapy (ERT) [21]

**Table 1.** Complications after allo-HSCT and their affecting organs & their symptoms [25]

| Organ | Diagnostic (sufficient to establish the diagnosis of chronic GVHD) | Distinctive | Other features |
|---|---|---|---|
| Skin | Poikiloderma Lichen planus like features Sclerotic features Morphea like features Lichen sclerosis-like features | Depigmentation | Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation |
| Nails | | Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis, nail loss | |
| Scalp and body hair | | New onset of scarring, scalp alopecia Scaling, papulosquamous lesions | Thinning scalp hair is typically patchy, course, or dull Premature grey hair |
| Mouth | Lichen type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis | Xerostomia Mucocele Mucosal atrophy Pseudomembranous ulcers | |
| Eyes | | New-onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Confluent areas of punctuating Keratopathy | Photophobia Periorbital Hyperpigmentation blepharitis |
| Genitalia | Lichen planus like features, vaginal scarring | Erosions Fissures Ulcers | |
| GI tract | Esophageal web strictures or stenosis in the upper to mid-third of the esophagus | | Exocrine pancreatic insufficiency |
| Lung | Bronchiolitis obliterans diagnosed with lung biopsy | Bronchiolitis obliterans diagnosed with PFTs and radiology | |
| Muscles | Facilities | Myositis or Polymyositis | Edema |
| Fascia, joints | Joint stiffness or contracture secondary to sclerosis | | Muscle cramps Arthralgia or arthritis |
| Hematopoietic and immune | | | Thrombocytopenia Eosinophilia Lymphopenia Hypo or hypergammaglobulinemia Autoantibodies |
| Other | | | Pericardial or pleural effusion Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction Abnormality or cardiomyopathy |

fraction. A lentiviral vector is used to add a normal ADA gene [23]. The cells are then formulated and certified. During this course of time, the patients receive some cytoreductive chemotherapy to make space for the stem cells, which are then reinfused intravenously, then those patients are studied for different endpoints for safety purposes and clinical outcomes, measuring the gene frequency, gene expression, and looking at the vector integration sites.

*Complications during Pre and Post Allogeneic*

Hematopoietic Stem Cells Transplantation Allogeneic hematopoietic stem cells transplantation is an effective therapy for various malignant and non-malignant

diseases. Though, allo-HSCT causes many complications that arise in stages, depending on the phase of treatment.

- Complications in the pre-transplant phase during the pre-transplant phase many side effects take place due to administration of high dose chemotherapy and radiation. These side effects include loss of hair, diarrhea, nausea, emesis, bladder infection, and mucositis [24].
- Complications in post-transplant phase complications after allo-HSCT mainly result from acute graft versus host disease. GVHD takes place due to mature T cells that in allograft can destroy malignant cells in the recipient. These T cells recognize the recipient as foreign and begin a wide range of immune mechanisms to attack recipient cells by a process known as graft versus host disease. Side effects include diarrhea, jaundice, nausea, emesis, bronchiolitis obliterans, alternation in sexual functioning and satisfaction, decrease in grip strength and knee extensor strength [24]. Patients undergoing allogenic-HSCT may have a low level of vitamin D, due to decreased exposure to sunlight, limited outdoor activity, and minimum oral intake that result in bone abnormalities. In table 1 is mentioned below, The list of complications after allo-HSCT and their affecting organs, symptoms have been mentioned [25].

## 3. TREATMENT

Allogenic hematopoietic stem cell transplantation causes acute graft versus host diseases due to mature T cells in the allograft, recognizing the recipient as foreign, and initiating a wide range of immune mechanisms to attack recipient cells in a process known as graft vs. host disease. In the previous clinical method, corticosteroid was administered to prevent and treat GVHD after alloHSCT. Administration of corticosteroids causes degradation of muscle proteins and inhibition of protein synthesis that leads to muscle atrophy. Patients experience a significant decrease in grip strength and knee extensor strength [24].

In recent clinical studies, human bone marrow-derived mesenchymal stem cell (hbmsc) derived exosomes have been applied in mice that attenuate acute graft versus host disease damage and promote the survival of GVHD mice by regulating dendritic cells and T-cell subpopulation and function and that lead to an inhibited inflammatory response in a GVHD mouse. Hence, we postulate that hbmsc-derived exosomes provide a potential, convenient and safe non-cell-based therapy to attenuate physiological responses to transplantation and eliminate the use of corticosteroids [25].

## 4. SURVIVAL

Allogenic hematopoietic stem cell transplantation is an effective therapy for various malignant and non-malignant diseases but associated with life-threatening complications.

About 10,632 records of patients worldwide reported to the center for international blood and marrow transplant research (CIBMTR) who was survived and disease-free 2 years after taking myeloablative allogeneic HCT before 2004 for acute lymphoblastic leukemia, myelodysplastic syndrome, lymphoma, or severe plastic anemia were analyzed.

In this analysis median follow-up was 9 years and 3,788 patients had been observed for 10 or more years. The probability of surviving 10 years after allo-HSCT was 85%. The risk factors for late death include Graft versus host diseases and old age. The common cause of death was relapse and patients who underwent transplantation for malignancy.

During the analysis of 6,691 survivors who received all-hematopoietic stem cells for severe aplastic anemia (SAA), acute lymphoblastic leukemia (ALL), acute

myelogenous leukemia (AML) who were alive recurrent disease-free at 2 years after HCT, survival at 5 years was 89%. The median follows up intervals were 9 years for AML (range 2-27 years), 9 years for AML (range 2-26 years), 8 years for MDS (range 2-20 years), 9 years for lymphoma (range 2-27 years) and 9 years for SAA (range 2-31 years).

The probabilities for being alive at 10 years after HCT were 84% for AML, 84% for lymphoma, 84% for ALL, 80% for MDS, and 92% for SAA. Those patients who underwent transplantation for malignancy, cumulative incidences of relapse at 10 years after HCT were 10% for AML, 9% for ALL, 10% for MDS, and 6% for lymphoma. Chances of disease-free survival at 10 years were 82% for AML, 82% for ALL, 78% for MDS, and 82% for lymphoma. Performance of hct earlier in the course of diseases, control of GVHD, enhancement of immune reconstitution, and prevention and early treatment of late complications are needed [27].

## 5. ALLOANTIGEN RECOGNITION AND RESPONSE TO ALLOGRAFT

Various end-stage diseases can be tackled by organ transplantation by the recent advances in cadaveric organ preservation techniques and chemotherapy involving immunosuppressive combination drugs. Even after increased allograft survival rates, chronic allograft rejection stays a major hindrance in the long-term acceptance of allograft in many transplant recipients. The significant reduction in the survival rates to less than 50% in five-year graft survivals is due to bronchiolitis obliterans which is followed by late graft failure [28].

The series of events that lead to chronic allograft rejection is initiated by T cells which recognize the alloantigen [29]. In the development of chronic allograft rejection, the major role is played by adaptive immunity. Two different mechanisms are known to occur when graft recipient CD4+ T cells respond to foreign antigens of grafted tissue. Donor cells express class II MHC-encoded molecules on their surface which get recognized by T cells quite frequently whereas class II MHC molecule bound polymorphic protein (minor histocompatibility antigen (mHAg)) from donor gets recognized by CD4+ T cells less frequently [30]. Earlier the direct identification of an imaging molecule was thought to be the major reason for acute graft but in the last decade, the chronic rejection was understood because of the CD4+ T cells which are reactive to mHAg activated indirectly. Skin allografts both class-I and Class II-deficient are found to be rejected by the graft recipients which are class I-deficient. It is found that after allotransplantation the frequency of CD 4 + t cells that can recognize donor-derived mHAg, can increase to 1-5% of total T cells in the spleen and blood of graft-recipient [31]. The functional importance of this increased frequency can be seen in the direct correlation between the existence of T cells that react against peptides in donors and lung graft dysfunction that is chronic [32].

After transplantation, lymph nodes of the graft recipient witness the entry of donor-derived mHAg due to cytolysis by alloantigen and accidental cell death. The complete cell which is derived from the transplanted tissue can also be engulfed by host APC. Identification of APC for CD4+ T cells or graft mHAg is difficult which are present in lymph nodes that drain the site of transplantation and are reactive to mHAg. The T cells that cause chronic damage of allograft and those that have a regulatory function and also prevent any further destruction to graft become identifiable by the characterization of T cells that are mHAg-reactive [28].

In experimental animals lacking T cells, the organ allograft perseveres for a long term despite any disparities due to donor-recipient MHC. However, these allografts undergo graft rejection after the transfer of T

cells which are allogeneic to the donor. As a result, T cell tolerance in recipients due to donor alloantigens causes bronchiolitis obliterans [33].

## 6. DIAGNOSIS

Several risk factors have been identified as having a strong link to the beginning of BOS, and the diagnosis of BOS entails a thorough examination of various post-transplant complications that can lead to delayed lung allograft failure. The efficacy of currently available drugs in preventing or treating BOS has yet to be established. Adequately designed and conducted randomized controlled trials with appropriately measured and reported all patient-important outcomes are essential to reveal appropriate therapy for established BOS and effective measures for its prevention. Inflammation, damage, and fibrosis of microscopic airways in the lung allograft are thought to be the cause of Bronchitis Obliterans Syndrome (BOS), which leads to obliterative bronchiolitis in many lung transplant recipients (OB). Because a definitive diagnosis of OB without a surgical lung biopsy is difficult, a decrease in FEV1 has been used as a surrogate marker to identify those who acquire a syndrome of significant and persistent loss of lung allograft function three months or more after transplantation. Several factors other than OB, however, can cause delayed onset of severe lung function loss, and these reasons for delayed onset graft failure must be thoroughly studied. It is ruled out when BOS is diagnosed. In general, BOS has a poor response to therapeutic methods, however with specific medicines, FEV1 may stabilize, and some patients may see a significant improvement.

The possibility of graft dysfunction and developing bronchiolitis obliterans syndrome is triggered by the decline in forced expiratory volume-1 (FEV1). By the moment FEV1 declines from the baseline value by 20%, the developing BOS may already have caused considerable damage to the allograft. All-inclusive evaluation to find out the cause of allograft dysfunction is initiated when clinically stable patients have symptoms like cough, fatigue, fever, or dyspnea, and also a major decline in FEV1 is observed on clinic visits or home spirometry [34].

Historically, lung biopsy was a preferred method of diagnosis, but now criteria of pulmonary function test (PFT) can be used in patients after HCT [35]. The recent definition of bronchiolitis obliterans consists of:

1. FEV1 prediction of <75% and in <2 years, an irreversible decline of ≥10%.
2. The ratio of FEV1 to vital capacity should be <0.7.
3. No occurrence of infection
4. Either of the following:
    - Previously diagnosed cGVHD
    - Diagnosis of air trapping by expiratory CT

Residual volume > 120% due to air trapping on pulmonary function tests or ratio of residual volume to total lung capacity that exceeds the confidence level by 90%.

The updated diagnostic criteria involved various requirements which suggest that patients with cGVHD and obstructive diseases need not essentially have air trapping, as this can be absent at early stages in the disease. The ratio of FEV1 to FVC of 0.7 was considered only for normal aged individuals, as children have a ratio of 1 and with age, it declines. Due to forced expiration, BOS patients' airway collapses which is why slow Vital capacity is used instead of forced vital capacity. To identify various severe diseases air trapping or expiratory CT scan is used but it is not required in the case of BOS. Patients with extra-pulmonary restriction are challenging to diagnose that may be because of GVHD myositis, polyneuritis, or steroid myopathy. Muscle weakness can be identified by expiratory pressures (EP) and maximum inspiratory pressures (MIP) [36].

Obliteration of large airways is a rare complication that has allo-immunity similar to BOS, diagnosed by bronchoscopy and treated with the help of lysis of webs. BOS can also occur without the setting of allogeneic hematopoietic stem cell transplantation. Frequently monitoring with the help of PFTs leads to the earliest diagnosis of the development of the disease [36].

Pleuroparenchymal changes along with air trapping can be effectively diagnosed with the help of high-resolution computed tomography (HRCT). The main cause of declining function or infection can be detected by using bronchoscopy with BAL and transbronchial lung biopsy (TBLB). Children below 4 years of age are unable to go through spirometry so it becomes challenging to screen them for any variation in lung function [34].

Absence of infection in the respiratory tract, as determined by clinical symptoms and, primarily, microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, bronchoalveolar lavage), though chest radiographs and computed tomographic (CT) scans can also be helpful.

A 6-minute walk test (6MWT), includes pulse oximetry and is defined as the distance a patient can walk in a 6-minute time, can help with early identification of BOS (primarily obstructive pattern). The 6MWT is the most often utilized test to determine whether or not a patient with BOS is responding to treatment. It is inexpensive and does not require the use of sophisticated technologies. The 6MWT has also been utilized as a one-time assessment of a patient's functional state and as a predictor of morbidity and mortality. A deteriorating 6MWT may identify people who require earlier or more intensive screening for BOS and maybe early intervention. Repeat testing at specific intervals could be highly effective.

Other modalities, such as parametric response mapping (PRM) of high-resolution helical CT images of the chest taken during inspiration and expiration, can detect restrictive or obstructive disease in patients who are unable to do PFTs, such as youngsters, or who are suffering from an infection. Because prospective data on this topic in HSCT is scarce, a practical unsolved challenge is the complicated diagnostic criteria and therapy of restrictive lung disease. In these circumstances, diagnostic criteria and treatment recommendations for idiopathic interstitial lung disorders may be used until more evidence on this entity is gathered.

*6.1. Availability of diagnostic modalities*

Although the current 2014 NIH cGVHD diagnostic criteria imply that CT scanning is not required for the diagnosis of BOS post-HCT, both PFTs and CT scans can be used to rule out other complicating illnesses, such as infections and other etiologies. Large tertiary care institutions have plenty of CT scanners for imaging, but the time it takes to receive a CT scan when there aren't enough, especially in developing countries and rural locations in Western countries, can cause considerable delays in diagnosis. According to recent research by the Organization for Economic Co-operation and Development (OECD), the number of CT scanners per million people (PMP) varies greatly, with Japan having 101.3 PMP CT scanners and Mexico having only 1.3 PMP CT scanners. This is exacerbated further by the fact that many patients in underdeveloped countries pay out of pocket because of the lack of a functioning public payer health system. According to a study released in 2001, the average cost of a CT scan in India was 45 US$ (1800 INR), while India's GDP per capita (nominal) was 471 US$. As a result, many patients are unable to obtain suitable tests promptly due to the test's high cost. PFTs at regular intervals after allogeneic HCT are a hot topic of study. However, the feasibility of this approach in some geographic areas (particularly in developing countries

where even hand-held spirometry is difficult to come by) is debatable [37].

*6.2. Biomarkers of BOS*

Significant success and advancement in curing the disease can be done if the timely identification of biomarkers is made which can predict the developing bronchiolitis obliterans at an early stage when allo-injury is more open to treatment. The use of assays is limited due to its inability to differentiate acute rejection, single lung transplantation from BOS. In the larger prospectus, any biomarker has not been validated for BOS. Studies have suggested that plasma osteopenia increases in BOS patients and the cause may be alveolar macrophages. Elevated levels are associated with even more critical conditions and diseases [36].

In lung transplant recipients that undergo BOS, it is observed that expansion of peripheral T cell clones takes place specifically among CD4 T cells that are unusually frequent. In the patients, even before the development of expiratory airflow, P incidents of clonal expansions were found [32]. To make monitoring of chronic allo-rejection intensity more, CD4 T cell clonality's surrogate markers have been examined. CD28 is a costimulatory molecule that is expressed on cell surfaces of CD4 T-lymphocytes of almost all normal humans. However, on repeated and regular clonal divisions of T cells, CD28 undergoes downregulation and their amount of CD28null T-cells is elevated in individuals that are suffering from chronic adaptive immune diseases. The pathogenic phenotype of the CD4+ CD28null cells is observed that lack CD28 cell surface. They start autonomous production of tumor necrosis factor (TNF)- α, IFN- α, expression of killer immunoglobulin-like receptors (KIR), perforin production which is a cytotoxic mediator, and granzyme B. These are not found in normal CD4 T cells [38].

Various pathogenic characters were also identified in a study in the recipients of lung transplants concerning CD4+ CD28null lymphocytes. Cyclosporine has various antiproliferative effects and it was found that these cells became resistant to it. Also, the elevated proportion of these cells caused worsening in prognosis in the lung transplant recipients. At the time of testing, the individuals which have normal spirometry may have also gone through clinical disruption and deterioration which can be predicted with the help of CD28 quantification [39]. Pathogenesis of BOS can be predicted by referring to the assays of peripheral T cells. It also helps in the prediction of approaching allograft injuries [29].

## 7. CONCLUSION

Allo-HSCT is an effective therapy to cure a wide range of patients with otherwise fatal diseases. However, patients undergoing allo-HSCT are exposed to long-term complications due to the administration of chemotherapy or radiation and corticosteroid. Recent clinical studies demonstrate that hematopoietic bone marrow mesenchymal stem cell-derived exosomes can attenuate a GVHD mice damage and increase the survival rate of GVHD mice by regulating the proportion of T-cell subpopulation and inhibiting inflammatory response in a GVHD mouse, which provided the potential of hbmsc-derived exosome as a convenient and safe non-cell-based therapy.

## 8. ACKNOWLEDGEMENT

NA

## 9. CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

## 10. SOURCE/S OF FUNDING

NA

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