

## Hematopoietic Stem Cell Research Literatures

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**Abstract:** The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

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**Key words:** stem cell; hematopoietic; life; research; literature

### Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell.

The following introduces recent reports as references in the related studies.

Al-Saud, B., H. Al-Mousa, et al. "Hematopoietic stem cell transplant for hyper-IgM syndrome due to CD40L defects: A single-center experience." *Pediatr Transplant*. 2015 Jun 13. doi: [10.1111/ptr.12538](https://doi.org/10.1111/ptr.12538).

HIGMI is a disease with a high risk for morbidity and mortality. HSCT has been shown to be a curative option. This study retrospectively reviewed and analyzed data from five patients who received HSCT at King Faisal Specialist Hospital & Research Centre (KFSH&RC) in Riyadh, Saudi Arabia, between 2005 and 2013. Five patients with HIGMI syndrome underwent HSCT at a median age of 41 months (range, 9-72 months). The median time from diagnosis to transplantation was 30 months (range, 5-58 months). For all five patients, the donors were HLA-identical siblings. In three patients, the conditioning regimen was composed of BU and CY. Fludarabine and melphalan with either ATG or alemtuzumab was used in two patients. For GVHD prophylaxis, cyclosporine was used in two patients, and the combination of cyclosporine and MTX was used in three patients. The survival rate was 100%, with a median follow-up of 69 months (range, 13-100 months). All patients engrafted. Two patients

developed acute GVHD. Four patients showed complete immune recovery with positive CD40L expression in activated T cells and discontinued IVIG replacement. HSCT in early stage from an HLA-matched sibling donor is potentially effective at curing the disease.

Arduino, P. G., C. Scully, et al. "Oral squamous cell carcinoma arising in a patient after hematopoietic stem cell transplantation with bisphosphonate-related osteonecrosis of the jaws." *Case Rep Dent*. 2015;2015:831418. doi: [10.1155/2015/831418](https://doi.org/10.1155/2015/831418). *Epub 2015 Apr 20*.

A 55-year-old man with a history of acute myeloid leukaemia treated with hematopoietic stem cell transplantation and with a 5-year history of bisphosphonate-related osteonecrosis of the jaws, following 12 cycles of intravenous zoledronic acid therapy, presented in December 2009 with a history of increasingly severe unilateral lower jaw pain. Oral examination revealed, as previously, exposed bone in the left mandible, but also a new exophytic mass on the lower-left buccal mucosa. Biopsy confirmed a diagnosis of oral squamous cell carcinoma. To the best of our knowledge, this is the first report of an oral squamous cell carcinoma that appeared adjacent to an area of osteochemonecrosis.

Asquith, J. M., J. Copacia, et al. "Successful use of reduced-intensity conditioning and matched-unrelated hematopoietic stem cell transplant in a child with Diamond-Blackfan anemia and cirrhosis." *Pediatr Transplant*. 2015 Jun 23. doi: [10.1111/ptr.12547](https://doi.org/10.1111/ptr.12547).

For patients with DBA who are transfusion dependent, HSCT is the only cure. Chronic transfusions can lead to cirrhosis secondary to iron overload, making them poor candidates for myeloablative HSCT. RIC regimens are associated

with lower morbidity and mortality compared to myeloablative regimens, but use of RIC in DBA has been limited. Here we present a 14-yr-old girl with DBA and multiple comorbidities including liver cirrhosis, who underwent MUD HSCT utilizing a RIC regimen that is novel to this condition. She tolerated the regimen well, and at 21 months, she remains transfusion independent with chimerisms at 99%.

Binsfeld, M., M. Hannon, et al. "Impact of the immunomodulating peptide thymosin alpha 1 on multiple myeloma and immune recovery after hematopoietic stem cell transplantation." Cancer Immunol Immunother. 2015 May 14.

Multiple myeloma (MM) is characterized by the accumulation of monoclonal plasma cells in the bone marrow and causes several immune alterations in patients. Thymosin alpha1 (Talpha1) is a thymic peptide that has been associated with immunostimulating properties. In addition, this peptide exerts anti-tumor effects in several cancer types. Beneficial effects of Talpha1 administration have also been shown on immune reconstitution after hematopoietic stem cell transplantation (HSCT), a current treatment modality in hematological malignancies including MM. In this study, we observed a slight reduction in the proliferation of murine and human MM cell lines in the presence of Talpha1 in vitro. However, using two immunocompetent murine MM models (5TGM1 and MOPC315.BM), we did not observe any impact of Talpha1 administration on MM development in vivo. Furthermore, no beneficial effects of Talpha1 treatment were observed on lymphocyte immune reconstitution after transfusion of human hematopoietic stem cells into immunodeficient mice. In conclusion, despite direct effects of Talpha1 on human MM cell line proliferation in vitro, Talpha1 did not exert anti-myeloma effects in vivo in the two murine models tested. Moreover, Talpha1 failed to improve immune recovery in a xenogeneic HSCT model.

Bizzarri, C., R. M. Pinto, et al. "Early and progressive insulin resistance in young, non-obese cancer survivors treated with hematopoietic stem cell transplantation." Pediatr Blood Cancer. 2015 May 27. doi: 10.1002/pbc.25603.

**BACKGROUND:** It is unclear whether there is a causative relationship between the development of metabolic syndrome (MS) and increased risk of early cardiovascular morbidity in patients receiving hematopoietic stem cell transplantation (HSCT) during childhood. Early identification of risk factors associated with insulin resistance, MS, and abnormal glucose tolerance during childhood or adolescence in these patients could represent a useful tool for

preventing cardiovascular disorders. **PROCEDURE:** In a single-center, prospective, descriptive, cross-sectional study, we studied 45 survivors of hematological malignancies (age: 13.9 +/- 4.8 years) treated with HSCT before the age of 18 years and 90 matched healthy controls. We collected clinical, imaging, and laboratory data including oral glucose tolerance test (OGTT). **RESULTS:** 7/45 patients (15.6%) showed abnormal glucose tolerance at OGTT, 1/45 (2.2%) was obese, and none fulfilled the criteria for MS. A waist/height ratio >0.5 was associated with patients with abnormal glucose tolerance (85.7% of cases), compared to patients with normal glucose tolerance (42.1%) and controls (23.3%). In patients with abnormal glucose tolerance, use of total body irradiation (TBI) as conditioning regimen was more common, and time elapsed from HSCT was longer. **CONCLUSIONS:** Patients treated with HSCT may develop insulin resistance early after transplantation. They do not show overt obesity, but have redistribution of fat tissue with central fat accumulation. The main factors associated with increased metabolic risk are TBI and time from HSCT. Evaluation of MS and glucose tolerance should be part of hormonal follow-up, which should be routinely proposed to these patients. *Pediatr Blood Cancer* (c) 2015 Wiley Periodicals, Inc.

Bogunia-Kubik, K., S. Mizia, et al. "Beneficial effect of the CXCL12-3'A variant for patients undergoing hematopoietic stem cell transplantation from unrelated donors." Cytokine. 2015 May 14. pii: S1043-4666(15)00171-4. doi: 10.1016/j.cyto.2015.05.001.

The present study aimed to assess the impact of the CXCL12 gene polymorphism (rs1801157) on clinical outcome of hematopoietic stem cell transplantation from unrelated donors. Toxic complications were less frequent among patients transplanted from donors carrying the CXCL12-3'-A allele (42/79 vs. 105/151, p=0.014 and 24/79 vs. 73/151, p=0.009, for grade II-IV and III-IV, respectively). Logistic regression analyses confirmed a role of donor A allele (OR=0.509, p=0.022 and OR=0.473, p=0.013 for grade II-IV and III-IV toxicity). In addition, age of recipients (OR=0.980, p=0.036 and OR=0.981, p=0.040, respectively) was independently protective while female to male transplantation and HLA compatibility were not significant. The incidence of aGvHD (grades I-IV) was lower in patients having A allele (52/119 vs. 113/204, p=0.043) and AA homozygous genotype (6/25 vs. 159/298, p=0.005). Independent associations of both genetic markers with a decreased risk of aGvHD were also seen in multivariate analyses (A allele: OR=0.591, p=0.030; AA homozygosity: OR=0.257, p=0.006) in which HLA compatibility

seemed to play less protective role ( $p < 0.1$ ) while recipient age and donor-recipient gender relation were not significant. Moreover, CXCL12-3'-A-positive patients were less prone to early HHV-6 reactivation (2/34 vs. 19/69,  $p = 0.026$ ). The presence of the CXCL12-3'-A variant was found to facilitate outcome of unrelated HSCT.

Brodzski, N., M. Svensson, et al. "Novel Genetic Mutations in the First Swedish Patient with Purine Nucleoside Phosphorylase Deficiency and Clinical Outcome After Hematopoietic Stem Cell Transplantation with HLA-Matched Unrelated Donor." *JIMD Rep.* 2015 May 13.

Purine nucleoside phosphorylase (PNP) is an enzyme active in the purine salvage pathway. PNP deficiency caused by autosomal recessive mutations in the PNP gene leads to severe combined immunodeficiency (SCID) and in two thirds of cases also to neurological effects such as developmental delay, ataxia, and motor impairment. PNP deficiency has a poor outcome, and the only curative treatment is allogeneic hematopoietic stem cell transplantation (HSCT). We present the first Swedish patient with PNP deficiency with novel mutations in the PNP gene and the immunological results of the HSCT and evaluate the impact of HSCT on the neurological symptoms. The patient presented early in life with neurological symptoms and suffered later from repeated serious respiratory tract infections. Biochemical tests showed severe reduction in PNP activity (1% residual activity). Genetic testing revealed two new mutations in the PNP gene: c.729C>G (p.Asn243Lys) and c.746A>C (p.Tyr249Cys). HSCT was performed with an unrelated donor, resulting in prompt and sustained engraftment and complete donor chimerism. There was no further aggravation of the patient's neurological symptoms at 21 months post HSCT, and appropriate developmental milestones were achieved. HSCT is curative for the immunological defect caused by PNP deficiency, and our case strengthens earlier reports that HSCT is effective as a treatment even for neurological symptoms in PNP deficiency.

Cessna, J. M., J. Pidala, et al. "Relationships between parenting self-efficacy and distress in parents who have school-aged children and have been treated with hematopoietic stem cell transplant or have no cancer history." *Psychooncology.* 2015 May 12. doi: [10.1002/pon.3848](https://doi.org/10.1002/pon.3848).

**OBJECTIVE:** Studies demonstrate that parents with cancer experience distress and that parenting self-efficacy (PSE) is related to distress among parents without cancer. However, no study to date has examined the relationships between PSE and

psychological distress among parents with cancer. This study sought to address this issue by comparing parents with cancer who had undergone hematopoietic stem cell transplantation (HSCT) to parents without cancer on measures of PSE and psychological distress. **METHODS:** A sample of 57 patients diagnosed with cancer who had undergone HSCT and a control group of 57 parents with no history of cancer were recruited for participation in the study. Medical record reviews assessed clinical variables, and participants filled out self-report measures of demographics, PSE, general self-efficacy, and psychological distress. **RESULTS:** As hypothesized, parents with cancer reported less PSE and more psychological distress than controls (all  $p$ -values  $\leq 0.05$ ). Furthermore, findings indicated that both PSE and general self-efficacy mediated the relationship between cancer status and psychological distress. **CONCLUSIONS:** Findings expand understanding of the potential sources of distress among parents with cancer who have been treated with HSCT and who have school-aged children. They also suggest that interventions aimed at reducing distress in these individuals should seek to target both parenting and general self-efficacy. Copyright (c) 2015 John Wiley & Sons, Ltd.

Chabannon, C., F. Bijou, et al. "A nationwide survey of the use of plerixafor in patients with lymphoid malignancies who mobilize poorly demonstrates the predominant use of the "on-demand" scheme of administration at French autologous hematopoietic stem cell transplant programs." *Transfusion.* 2015 May 13. doi: [10.1111/trf.13141](https://doi.org/10.1111/trf.13141).

**BACKGROUND:** High-dose chemotherapy supported with autologous stem cell transplantation is a standard therapeutic option for a subset of patients with lymphoid malignancies. Cell procurement is nowadays done almost exclusively through cytopheresis, after mobilization of hematopoietic stem and progenitor cells (HSPCs) from the marrow to peripheral blood (PB). The egress of HSPCs out of hematopoietic niches occurs in various physiologic or nonhomeostatic situations; pharmacologic approaches include the administration of acutely myelosuppressive agents or hematopoietic growth factors such as recombinant human granulocyte-colony-stimulating factor (rHuG-CSF). The introduction of plerixafor, a first-of-its-class molecule that reversibly inhibits the interaction between the chemokine CXCL-12 (also known as SDF-1) and its receptor CXCR-4, has offered new opportunities for the so-called "poor mobilizers" who achieve insufficient mobilization and/or collection with conventional approaches. **STUDY DESIGN AND METHODS:** Because of the lack of consensus on a definition for poor mobilizers and the relatively high

cost of plerixafor, French competent authorities have mandated a postmarketing survey on its use in routine practice. **RESULTS AND CONCLUSION:** We report here the results of this nationwide survey that confirms the clinical efficacy of plerixafor, even in the subset of patients who barely increased PB CD34+ cell count in response to rHuG-CSF-containing mobilization regimen. Furthermore, analysis of this registry showed that despite heterogeneity in medical practices, the early-"on-demand" or "preemptive"-introduction of plerixafor was widely used and did not result in an excess of prescriptions, beyond its expected use at the time when marketing authorization was granted.

Chopra, M., A. Brandl, et al. "Blocking TWEAK-Fn14 interaction inhibits hematopoietic stem cell transplantation-induced intestinal cell death and reduces GvHD." *Blood*. 2015 May 26. pii: [blood-2015-01-620583](https://doi.org/10.1182/blood-2015-01-620583).

Inhibition of the TWEAK/Fn14 system reduces intestinal cell death and disease development in several models of colitis. In view of the crucial role of TNF and intestinal cell death in graft-versus-host-disease (GvHD) and the ability of TWEAK to enhance TNF-induced cell death, we tested here the therapeutic potential of Fn14 blockade on allogeneic hematopoietic cell transplantation (allo-HCT) induced intestinal GvHD. A Fn14-specific blocking human IgG1 antibody variant with compromised antibody-dependent cellular cytotoxicity (ADCC) activity strongly inhibited the severity of murine allo-HCT induced GvHD. Treatment of the allo-HCT recipients with this mAb reduced cell death of gastrointestinal cells but neither affected organ infiltration by donor T-cells nor cytokine production. Fn14 blockade also inhibited intestinal cell death in mice challenged with TNF. This suggests that the protective effect of Fn14 blockade in allo-HCT is based on the protection of intestinal cells from TNF-induced apoptosis and not due to immune suppression. Importantly, Fn14 blockade showed no negative effect on graft-versus-lymphoma (GvL) activity. Thus, ADCC-defective Fn14-blocking antibodies are not only possible novel GvL effect-sparing therapeutics for the treatment of GvHD but might also be useful for the treatment of other inflammatory bowel diseases where TNF-induced cell death is of relevance.

Cieri, N., R. Greco, et al. "Post-transplantation Cyclophosphamide and Sirolimus after Haploidentical Hematopoietic Stem Cell Transplantation Using a Treosulfan-based Myeloablative Conditioning and Peripheral Blood Stem Cells." *Biol Blood Marrow Transplant*. 2015 May 19. pii: [S1083-8791\(15\)00321-3](https://doi.org/10.1016/j.bbmt.2015.04.025). doi: [10.1016/j.bbmt.2015.04.025](https://doi.org/10.1016/j.bbmt.2015.04.025).

Haploidentical hematopoietic stem cell transplantation (HSCT) performed using bone marrow (BM) grafts and post-transplantation cyclophosphamide (PTCy) has gained much interest for the excellent toxicity profile after both reduced-intensity and myeloablative conditioning. We investigated, in a cohort of 40 high-risk hematological patients, the feasibility of peripheral blood stem cells grafts after a treosulfan-melphalan myeloablative conditioning, followed by a PTCy and sirolimus-based graft-versus-host disease (GVHD) prophylaxis (Sir-PTCy). Donor engraftment occurred in all patients, with full donor chimerism achieved by day 30. Post-HSCT recovery of lymphocyte subsets was broad and fast, with a median time to CD4 > 200/μL of 41 days. Cumulative incidences of grade II to IV and III-IV acute GVHD were 15% and 7.5%, respectively, and were associated with a significant early increase in circulating regulatory T cells at day 15 after HSCT, with values < 5% being predictive of subsequent GVHD occurrence. The 1-year cumulative incidence of chronic GVHD was 20%. Nonrelapse mortality (NRM) at 100 days and 1 year were 12% and 17%, respectively. With a median follow-up for living patients of 15 months, the estimated 1-year overall and disease-free survival (DFS) was 56% and 48%, respectively. Outcomes were more favorable in patients who underwent transplantation in complete remission (1-year DFS 71%) versus patients who underwent transplantation with active disease (DFS, 34%; P = .01). Overall, myeloablative haploidentical HSCT with peripheral blood stem cells (PBSC) and Sir-PTCy is a feasible treatment option: the low rates of GVHD and NRM as well as the favorable immune reconstitution profile pave the way for a prospective comparative trial comparing BM and PBSC in this specific transplantation setting.

Gama, I., W. Rodrigues, et al. "Chronic Ocular Graft vs Host Disease as a Serious Complication of Allogeneic Hematopoietic Stem Cell Transplantation: Case Report." *Transplant Proc*. 2015 May;47(4):1059-62. doi: [10.1016/j.transproceed.2015.03.038](https://doi.org/10.1016/j.transproceed.2015.03.038).

Chronic graft-vs-host disease (cGVHD) is a serious systemic immunological complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Ocular GVHD (O-GVHD) is frequently associated with cGVHD. Secondary corneal epithelial changes can occur in the setting of advanced chronic O-GVHD-associated keratoconjunctivitis sicca (KCS), which generally has a stable course with conventional medical treatment. Bilateral corneal ulcers and ocular perforation, although not frequent, can occur in most extreme cases. The authors describe 2 clinical cases of ocular perforation (Clinical case 1) and bilateral simultaneous corneal ulcers (Clinical case 2) due to

advanced chronic O-GVHD, which can rarely occur despite treatment. A close ophthalmological follow-up and good dialogue with the multidisciplinary transplantation team are essential after allo-HSCT.

Garcia, E., D. Buenasmananas, et al. "[Sirolimus associated pneumonitis in a hematopoietic stem cell transplant patient]." *Med Clin (Barc)*. 2015 Jul 6;145(1):21-3. doi: 10.1016/j.medcli.2015.02.025. Epub 2015 May 12.

**BACKGROUND AND OBJECTIVE:** Sirolimus (SR) is a lipophilic macrocyclic lactone with immunosuppressive properties (mTOR inhibitor) commonly used in solid organ transplantation and recently introduced in the prophylaxis and treatment of graft-versus-host disease. Its numerous side effects include: hyperlipidemia, arthralgias, noncardiac peripheral edema, thrombotic microangiopathy and interstitial pneumonitis. SR-associated pneumonitis is a rare but potentially serious complication due to its increasing utilization in transplant patients. **PATIENT AND METHOD:** We report the case of a patient undergoing hematopoietic stem cell transplantation with severe respiratory distress and SR therapy. **RESULTS:** Microbiological tests were all negative and other complications related to transplantation were discarded. The chest computed tomography of high-resolution showed pneumonitis. The SR therapy was interrupted and treatment was started with steroids with resolution of symptoms. **CONCLUSIONS:** SR associated pneumonitis is a potentially fatal side effect. In patients treated with SR and respiratory failure, we must suspect this complication because early recognition along with drug discontinuation and steroid treatment is essential to reverse this complication.

Hakki, M., R. M. Rattray, et al. "The clinical impact of coronavirus infection in patients with hematologic malignancies and hematopoietic stem cell transplant recipients." *J Clin Virol*. 2015 Jul;68:1-5. doi: 10.1016/j.jcv.2015.04.012. Epub 2015 Apr 15.

**BACKGROUND:** Compared to other respiratory viruses, relatively little is known about the clinical impact of coronavirus (CoV) infection after hematopoietic stem cell transplant (HSCT) or in patients with hematologic malignancies. **OBJECTIVES:** To characterize the role of CoV in respiratory tract infections among HSCT and hematologic malignancy patients. **STUDY DESIGN:** We conducted a retrospective review of all cases of CoV infection documented by polymerase chain reaction, (PCR)-based testing on nasopharyngeal and bronchoalveolar lavage fluid samples between June 2010 and 2013. Cases of CoV infection occurring in HSCT and hematologic malignancy patients were

identified and the clinical characteristics of these cases were compared to other respiratory viruses. **RESULTS:** CoV was identified in 2.6% (n=43) of all samples analyzed (n=1661) and in 6.8% of all samples testing positive for a respiratory virus (n=631). 33 of 38 (86.8%) of patients in whom CoV was identified were HSCT and hematologic malignancy patients. Among these patients, CoV was detected in 9.7% of unique infection episodes, with only rhinovirus/enterovirus (RhV/EnV) infection being more common. Group I CoV subtypes accounted for 76.3% of cases, and 57% of infections were diagnosed between December and March. CoV infection was associated with upper respiratory tract symptoms in most patients, similar to other respiratory viruses. Possible and proven lower respiratory tract disease was less common compared to other respiratory viruses except RhV/EnV. **CONCLUSIONS:** CoV is frequently detected in HSCT and hematologic malignancy patients in whom suspicion for a respiratory viral infection exists, but is less likely to progress to lower respiratory tract disease than most other respiratory viruses.

Iancu-Rubin, C. and R. Hoffman "Role of epigenetic reprogramming in hematopoietic stem cell function." *Curr Opin Hematol*. 2015 Jul;22(4):279-85. doi: 10.1097/MOH.0000000000000143.

**PURPOSE OF REVIEW:** Epigenetic regulatory networks determine the fate of dividing hematopoietic stem cells (HSCs). Prior attempts at the ex-vivo expansion of transplantable human HSCs have led to the depletion or at best maintenance of the numbers of HSCs because of the epigenetic events that silence the HSC gene-expression pattern. The purpose of this review is to outline the recent efforts to use small molecules to reprogram cultured CD34 cells so as to expand their numbers. **RECENT FINDINGS:** Chromatin-modifying agents (CMAs) reactivate the gene-expression patterns of HSCs that have been silenced as they divide ex vivo. Increasing evidence indicates that CMAs act not only by promoting HSC symmetrical self-renewal divisions, but also by reprogramming progenitor cells, resulting in greater numbers of HSCs. The use of such CMAs for these purposes has not resulted in malignant transformation of the ex-vivo treated cell product. **SUMMARY:** The silencing of the gene-expression program that determines HSC function after ex-vivo culture can be reversed by reprogramming the progeny of dividing HSCs with transient exposure to CMAs. The successful implementation of this approach provides a strategy which might lead to the development of a clinically relevant means of manufacturing increased numbers of HSCs.

Ikegawa, S., N. Doki, et al. "Allogeneic hematopoietic stem cell transplantation (allo-HSCT) overcomes poor prognosis of acute myeloid leukemia with myelodysplasia-related changes (AML-MRC)." *Leuk Lymphoma*. 2015 Jun 18:1-21.

Recent studies have shown that acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) exhibits a worse clinical outcome than AML not otherwise specified (AML-NOS). However, transplant outcomes of patients with AML-MRC have not been reported compared to patients with AML-NOS. We analyzed transplant outcomes among 147 patients with AML-MRC or AML-NOS who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) in a single institution. There were no significant differences in the 2-year overall survival, cumulative incidence of relapse, and non-relapse mortality between the two groups (2-year OS: 48% vs. 59%; 2-year CIR: 37% vs. 35%; 2-year NRM: 19% vs. 13%). Subgroup analysis adjusting for age and disease status demonstrated the same results between the two groups. Furthermore, multivariate analysis showed that AML-MRC was not an independent prognostic factor for poor prognosis in the setting of allo-HSCT ( $p = 0.7$ ). These results suggest that allo-HSCT may overcome the poor prognosis of AML-MRC.

Inagaki, J., Y. Kodama, et al. "Mycophenolate mofetil for treatment of steroid-refractory acute graft-versus-host disease after pediatric hematopoietic stem cell transplantation." *Pediatr Transplant*. 2015 Jun 23. doi: [10.1111/ptr.12545](https://doi.org/10.1111/ptr.12545).

A standard treatment is yet to be established for steroid-refractory acute aGVHD following HSCT. The effects of MMF have not been well studied in children with aGVHD. We evaluated the effectiveness of oral MMF in 14 children with steroid-refractory aGVHD (grade II in one patient, grade III to IV in 13 patients). The median initial dose of MMF was 40 mg/kg/day (range, 30-74) and was increased by 1.5-2 times if manifestations of GVHD did not improve. Within four wk of treatment, seven patients (50%) achieved CR, and four (29%) had a PR. Within eight wk, 11 patients (79%) achieved CR without using additional agents. Overall, 12 patients are alive and in remission with a median follow-up of 35 months (range, 14-86). The median maximum dose of MMF was 60 mg/kg/day (range, 34-107). No fatal toxicity was observed, including MMF-related infections. MMF appears to be highly effective for steroid-refractory aGVHD when used at a higher dose than has been described previously. Larger studies and pharmacokinetic analysis are required to evaluate its efficacy and toxicity and find the optimal dose of MMF in children.

Kaida, K., K. Ikegame, et al. "Pharmacokinetics of 8 mg/kg anti-human T-lymphocyte rabbit immunoglobulin conditioning for hematopoietic stem cell transplantation in Japanese patients." *Rinsho Ketsueki*. 2015;56(5):475-80. doi: [10.11406/rinketsu.56.475](https://doi.org/10.11406/rinketsu.56.475).

Anti-human T-lymphocyte immunoglobulin, rabbit (ATG, Zetbulin((R)) intravenous infusion liquid), is an immunosuppressive agent that is indicated for aplastic anemia in Japan. The "prevention of graft-versus-host disease (GVHD) for allogeneic hematopoietic stem cell transplantation in adults" indication has been added to ATG in 32 countries worldwide, but has not yet been approved for GVHD prevention in Japan. The pharmacokinetics of ATG in Japanese people has not yet been assessed. In this study, to assess ATG pharmacokinetics, ATG (2 mg/kg/day from day-4 to day-1) as a pretransplant treatment was administered to six patients who had received transplantation of HLA-haploidentical stem cells. The ATG concentration was measured using an ELISA kit for rabbit IgG. The serum ATG concentration increased with administration for 4 consecutive days, peaking at a concentration of 66.0μg/ml (+/-8.8 SD). Subsequently, it gradually decreased with an elimination half-life of 21.9 days (+/-20.4 SD) but was still detectable in serum even a few weeks after allogeneic hematopoietic stem cell transplantation. We found the pharmacokinetics of ATG in this study to be comparable to those described in previous reports from Europe.

Kawamura, K., J. Hayakawa, et al. "Low-dose acyclovir prophylaxis for the prevention of herpes simplex virus and varicella zoster virus diseases after autologous hematopoietic stem cell transplantation." *Int J Hematol*. 2015 May 20.

Limited data are available on prophylaxis for herpes simplex virus (HSV) and varicella zoster virus (VZV) disease following autologous hematopoietic stem cell transplantation (auto-HCT). We retrospectively reviewed the clinical charts of 105 consecutive patients who underwent their first auto-HCT at our institution between September 2007 and June 2014. Before August 2009, 30 patients received oral acyclovir at 1000 mg/day until engraftment, whereas after September 2009, 69 patients received oral acyclovir at 200 mg/day. After engraftment, acyclovir was continued at 200 mg/day at the discretion of the attending physicians in both groups. The cumulative incidence of HSV disease at 1 year after auto-HCT was 7.7 and 4.5 % in patients who received oral acyclovir at 1000 and 200 mg/day, respectively ( $P = 0.75$ ). Patients were next divided into three groups according to the timing at which

acyclovir prophylaxis was stopped after auto-HCT; at engraftment, between engraftment and 1 year after auto-HCT, and later than 1 year. The cumulative incidence of VZV disease was 25.8, 7.7, and 0.0 % at 1 year, respectively. This study suggests that low-dose acyclovir prophylaxis may be effective for preventing HSV and VZV disease after auto-HCT. Our findings support the recommendation of acyclovir prophylaxis within the first year after auto-HCT.

Khosravi, M., M. Izaddoust, et al. "Association of GSTO2 (N142D), GSTT1, and GSTM1 Polymorphisms With Graft-Versus-Host Disease in Allogeneic Hematopoietic Stem Cell Transplant Recipients." *Exp Clin Transplant*. 2015 Jun 15. doi: [10.6002/ect.2014.0111](https://doi.org/10.6002/ect.2014.0111).

**OBJECTIVES:** Graft-versus-host disease is a major problem after bone marrow transplant. GSTM1, GSTT1, and GSTO2 are important genes that interfere with xenobiotic and drug metabolism. Polymorphisms of these genes may influence the metabolism of immunosuppressive drugs given for inhibition of graft-versus-host disease and may influence their susceptibility to diseases, which bone marrow transplant could alleviate. **MATERIALS AND METHODS:** We examined the polymorphisms of 2 groups: The first group was composed of 88 patients who had undergone a bone marrow transplant and 100 otherwise healthy persons; the second group was composed of 54 patients without graft-versus-host disease and 34 patients with graft-versus-host disease. We used polymerase chain reaction-restriction fragment length polymorphism method for genotyping GSTO2 and also for multiplexing polymerase chain reactions for GSTT1 and GSTM1 genotypes. **RESULTS:** No significant association existed between the genotypes GSTO2 (DD:  $P = .458$ , OR 0.422), GSTM1 ( $P = .349$ , OR 1.52), or GSTT1 ( $P = .887$ , OR 1.086), and the incidence of GVHD. Moreover, we saw no association between these polymorphisms and the problems that lead to bone marrow transplant (GSTO2: DD,  $P = .181$ , OR 0.465; GSTM1:  $P = .699$ , OR 0.892; GSTT1:  $P = .656$ , OR 0.845). We showed that men have more bone marrow transplants than do women ( $P = .019$ , OR 2.034). **CONCLUSIONS:** Our results show that these poly-morphisms may have no effect on the metabolism of drugs used to treat graft-versus-host disease and also, may play no significant role in creating the problems that lead to bone marrow transplant.

Lassiter, M. and S. M. Schneider "A pilot study comparing the neutropenic diet to a non-neutropenic diet in the allogeneic hematopoietic stem cell transplantation population." *Clin J Oncol Nurs*. 2015 Jun 1;19(3):273-8. doi: [10.1188/15.CJON.19-03AP](https://doi.org/10.1188/15.CJON.19-03AP).

**BACKGROUND:** Historically, dietary restrictions imposed on patients undergoing hematopoietic stem cell transplantation (HSCT) were severe and limited to prevent exposure to foodborne organisms. With improvements in supportive care and anti-infective agents, the necessity of the neutropenic diet for this population has been in question. **OBJECTIVES:** This study aimed to determine whether the incidence of infection differs and to analyze the nutritional status in patients undergoing myeloablative allogeneic HSCT with a neutropenic diet as compared to those with a diet without restrictions. **METHODS:** This study was a randomized, controlled prospective pilot study beginning within the first 24 hours of the start of the conditioning regimen. Patients were randomized to receive a neutropenic diet or a diet without restrictions. All patients received care in a high-efficiency particulate air-filtered room on the inpatient adult blood and marrow transplantation unit (ABMTU). All patients received antibacterial and antifungal prophylaxis. Patients were followed until the end of neutropenia (defined as absolute neutrophil count of greater than 500 for three days) or until discharge from the inpatient ABMTU. **FINDINGS:** In 46 evaluable patients, no significant difference was found between infection rates or nutritional status. The neutropenic diet did not offer a protective effect against infection in patients undergoing myeloablative allogeneic HSCT. No differences were found in nutritional status between the two groups.

Maecker-Kolhoff, B. and B. Eiz-Vesper "Broad spectrum antiviral T cells for viral complications after hematopoietic stem cell transplantation." *Ann Transl Med*. 2015 May;3(Suppl 1):S4. doi: [10.3978/j.issn.2305-5839.2015.01.30](https://doi.org/10.3978/j.issn.2305-5839.2015.01.30).

Major complications of hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT), such as graft rejection and graft-versus-host-disease (GvHD), are countered by suppressing the host immune system via chemotherapy and radiation, immunosuppressive drugs, or conditioning regimens such as in vivo or in vitro T-cell depletion. While immunocompromised, the patient is rendered susceptible to a number of viral infections and reactivations mainly caused by endogenous herpes viruses like cytomegalovirus (CMV) and Epstein-Barr virus (EBV) and by lytic agents such as adenovirus (ADV). In the paper entitled "Activity of broad-spectrum T cells as treatment for ADV, EBV, CMV, BKV, and HHV6 Infections after HSCT" published recently in *Science Translational Medicine*, Anastasia Papadopoulou and colleagues reported a suitable technology for rapid generation of antiviral T cells with a broad specificity

in a single-culture for clinical application. In a small clinical trial with 11 patients they demonstrated safety and efficacy of adoptive multivirus-specific T-cell transfer.

Majorana, A., F. Amadori, et al. "Taste dysfunction in patients undergoing hematopoietic stem cell transplantation: Clinical evaluation in children." *Pediatr Transplant.* 2015 Jun 5. doi: [10.1111/ptr.12535](https://doi.org/10.1111/ptr.12535).

The aim of this study was to determine the variability of TD in children undergoing HSCT. Cases were identified as consecutively enrolled children in the period January 2011-January 2013 among patients attending the Paediatric Department of Spedali Civili of Brescia and all candidates to HSCT. The TST was conducted in two phases: identification of threshold values and identification of perceived stimulus intensity. Sixteen sapid solutions with four flavors (sucrose, sodium chloride, citric acid, and quinine hydrochloride) at four different concentrations were administered in a random sequence. The same protocol was administered at different time intervals: before starting the conditioning therapy (T0), during the conditioning therapy (T1) (two times), and every three months (two times) after engraftment post-HSCT (T2). A p-value < 0.05 was considered statistically significant. Fifty-one children (29 female and 22 male, mean age 5.2 +/- 0.7 yr) were enrolled. Threshold value means for the four flavors increased during HSCT conditioning therapy (T1) (p < 0.01); intensity of perceived stimulus decreased during HSCT conditioning therapy (p < 0.01). At six months after engraftment (T2), both parameters had returned to starting values (T0). Changes in taste perception in children undergoing HSCT seem to occur especially during the conditioning therapy and resolve in about six months after engraftment post-HSCT.

Mantel, C. R., H. A. O'Leary, et al. "Enhancing Hematopoietic Stem Cell Transplantation Efficacy by Mitigating Oxygen Shock." *Cell.* 2015 Jun 18;161(7):1553-65. doi: [10.1016/j.cell.2015.04.054](https://doi.org/10.1016/j.cell.2015.04.054). Epub 2015 Jun 11.

Hematopoietic stem cells (HSCs) reside in hypoxic niches within bone marrow and cord blood. Yet, essentially all HSC studies have been performed with cells isolated and processed in non-physiologic ambient air. By collecting and manipulating bone marrow and cord blood in native conditions of hypoxia, we demonstrate that brief exposure to ambient oxygen decreases recovery of long-term repopulating HSCs and increases progenitor cells, a phenomenon we term extraphysiologic oxygen shock/stress (EPOSS). Thus, true numbers of HSCs in the bone marrow and cord blood are routinely

underestimated. We linked ROS production and induction of the mitochondrial permeability transition pore (MPTP) via cyclophilin D and p53 as mechanisms of EPOSS. The MPTP inhibitor cyclosporin A protects mouse bone marrow and human cord blood HSCs from EPOSS during collection in air, resulting in increased recovery of transplantable HSCs. Mitigating EPOSS during cell collection and processing by pharmacological means may be clinically advantageous for transplantation.

Masetti, R., D. Zama, et al. "Impact of inflammatory cytokine gene polymorphisms on developing acute graft-versus-host disease in children undergoing allogeneic hematopoietic stem cell transplantation." *J Immunol Res.* 2015;2015:248264. doi: [10.1155/2015/248264](https://doi.org/10.1155/2015/248264). Epub 2015 Apr 20.

Single nucleotide polymorphisms (SNPs) in gene encoding pro- and anti-inflammatory factors have been associated with the occurrence of aGvHD. We retrospectively tested a wide panel of 38 polymorphisms in 19 immunoregulatory genes, aiming to first establish, in a pediatric HSCT setting, which SNPs were significantly associated with the development of aGvHD. A significant association was found between aGvHD grades II-IV and SNPs of donor IL10-1082GG, and Fas-670CC + CT and recipient IL18-607 TT + TG genotype. aGvHD grades III-IV resulted associated with donor IL10-1082GG, Fas-670CC + CT, and TLR4-3612TT as well as the use of peripheral CD34+ cells as stem cell source. The multivariate analysis confirmed the association between donor IL10-1082GG and Fas-670CC + CT and aGvHD grades II-IV and between donor IL10-1082GG and TLR4-3612TT and aGvHD grades III-IV. In conclusion we found an association between IL10, FAS, and TLR4 in the donor and IL18 in the recipient and an increased risk of developing aGvHD in transplanted children. Knowledge of the SNPs of cytokine genes associated with aGvHD represents a useful tool for an integrated pretransplantation risk assessment and could guide the physicians to an optimal and more accurate HSCT planning.

McDonald, L. T., D. L. Russell, et al. "Hematopoietic stem cell-derived cancer-associated fibroblasts are novel contributors to the pro-tumorigenic microenvironment." *Neoplasia.* 2015 May;17(5):434-48. doi: [10.1016/j.neo.2015.04.004](https://doi.org/10.1016/j.neo.2015.04.004).

Targeting the tumor microenvironment is critical toward improving the effectiveness of cancer therapeutics. Cancer-associated fibroblasts (CAFs) are one of the most abundant cell types of the tumor microenvironment, playing an important role in tumor progression. Multiple origins for CAFs have been proposed including resident fibroblasts, adipocytes,

and bone marrow. Our laboratory previously identified a novel hematopoietic stem cell (HSC) origin for CAFs; however, the functional roles of HSC-derived CAFs (HSC-CAFs) in tumor progression have not yet been examined. To test the hypothesis that HSC-CAFs promote tumor progression through contribution to extracellular matrix (ECM) and paracrine production of pro-angiogenic factors, we developed a method to isolate HSC-CAFs. HSC-CAFs were profiled on the basis of their expression of hematopoietic and fibroblastic markers in two murine tumor models. Profiling revealed production of factors associated with ECM deposition and remodeling. Functional in vivo studies showed that co-injection of HSC-CAFs with tumor cells resulted in increased tumor growth rate and significantly larger tumors than tumor cells alone. Immunohistochemical studies revealed increased blood vessel density with co-injection, demonstrating a role for HSC-CAFs in tumor vascularization. Mechanistic in vitro studies indicated that HSC-CAFs play a role in producing vascular endothelial growth factor A and transforming growth factor-beta1 in endothelial tube formation and patterning. In vitro and in vivo findings suggest that HSC-CAFs are a critical component of the tumor microenvironment and suggest that targeting the novel HSC-CAF may be a promising therapeutic strategy.

Mehta, A., J. L. Zhao, et al. "The MicroRNA-132 and MicroRNA-212 Cluster Regulates Hematopoietic Stem Cell Maintenance and Survival with Age by Buffering FOXO3 Expression." *Immunity*. 2015 Jun 16;42(6):1021-32. doi: 10.1016/j.immuni.2015.05.017.

MicroRNAs are critical post-transcriptional regulators of hematopoietic cell-fate decisions, though little remains known about their role in aging hematopoietic stem cells (HSCs). We found that the microRNA-212/132 cluster (Mirc19) is enriched in HSCs and is upregulated during aging. Both overexpression and deletion of microRNAs in this cluster leads to inappropriate hematopoiesis with age. Enforced expression of miR-132 in the bone marrow of mice led to rapid HSC cycling and depletion. A genetic deletion of Mirc19 in mice resulted in HSCs that had altered cycling, function, and survival in response to growth factor starvation. We found that miR-132 exerted its effect on aging HSCs by targeting the transcription factor FOXO3, a known aging associated gene. Our data demonstrate that Mirc19 plays a role in maintaining balanced hematopoietic output by buffering FOXO3 expression. We have thus identified it as a potential target that might play a role in age-related hematopoietic defects.

Mendorf, A., E. Klyuchnikov, et al. "Atovaquone for Prophylaxis of Toxoplasmosis after Allogeneic Hematopoietic Stem Cell Transplantation." *Acta Haematol.* 2015 May 5;134(3):146-154.

Toxoplasmosis and infections by other opportunistic agents such as *Pneumocystis jirovecii* constitute life-threatening risks for patients after allogeneic hematopoietic stem cell transplantation. Trimethoprim/sulfamethoxazole (TMP-SMX) has been well established for post-transplant toxoplasmosis and pneumocystis prophylaxis, but treatment may be limited due to toxicity. We explored atovaquone as an alternative and compared it with TMP-SMX regarding toxicity and efficacy during the first 100 days after transplantation in 155 consecutive adult stem cell recipients. Eight patients with a prior history of TMP-SMX intolerance received atovaquone as first-line prophylaxis. TMP-SMX was used for 141 patients as first-line strategy, but 13 patients (9.2%) were later switched to atovaquone due to TMP-SMX toxicity or gastrointestinal symptoms. No active toxoplasmosis or active *P. jirovecii* infection developed under continued prophylaxis with either TMP-SMX or atovaquone. However, for reasons of TMP-SMX and/or atovaquone toxicity, 7 patients were unable to tolerate any efficacious toxoplasmosis prophylaxis and therefore obtained inhalative pentamidine as *P. jirovecii* prophylaxis but no toxoplasmosis prophylaxis. Importantly, 2 of these patients developed severe toxoplasmosis. In summary, atovaquone appears as a valid alternative for at least some post-transplant patients who cannot tolerate TMP-SMX. This should be further confirmed by multicenter trials. (c) 2015 S. Karger AG, Basel.

Miyagi, T., H. Itonaga, et al. "Successful treatment of toxoplasmic encephalitis diagnosed early by polymerase chain reaction after allogeneic hematopoietic stem cell transplantation: two case reports and review of the literature." *Transpl Infect Dis.* 2015 May 13. doi: 10.1111/tid.12401.

Toxoplasmic encephalitis represents a rare, but often fatal infection after allogeneic hematopoietic stem cell transplantation. Polymerase chain reaction (PCR)-based preemptive therapy is considered promising for this disease, but is not routinely applied, especially in low seroprevalence countries including Japan. We encountered 2 cases of toxoplasmic encephalitis after transplantation that were successfully treated. The diagnosis of toxoplasmic encephalitis in these cases was confirmed by PCR testing when neurological symptoms were observed. Both patients received pyrimethamine and sulfadiazine treatments within 2 weeks of the development of neurological symptoms, and remained free of recurrence for 32 and 12 months. These results

emphasized the importance of the PCR test and immediate treatment after diagnosis for the management of toxoplasmic encephalitis. This article is protected by copyright. All rights reserved.

Neemann, K. and A. Freifeld "Respiratory Syncytial Virus in Hematopoietic Stem Cell Transplantation and Solid-Organ Transplantation." Curr Infect Dis Rep. 2015 Jul;17(7):490. doi: 10.1007/s11908-015-0490-9.

Respiratory syncytial virus (RSV), one of the most common causes of respiratory infections in immunocompetent individuals, can cause significant pulmonary morbidity and mortality in hematopoietic stem cell (HSCT) and less often in solid-organ transplant recipients. Early diagnosis and medical intervention prior to the progression from upper to lower respiratory tract viral involvement is essential to positively affect the clinical course. The greatest risk of disease progression from upper to lower respiratory tract disease is during the early posttransplant period for HSCT recipients, with lymphopenia being an important risk factor. Polymerase chain reaction has become the preferred method for rapidly diagnosing infection in this population because of higher sensitivity compared to traditional viral culture and direct viral antigen methods. Despite the lack of prospective randomized trials, retrospective pooled analyses have suggested that systemically delivered ribavirin (either aerosolized, oral, or IV; with or without immunomodulator therapy) can decrease the risk of progression of disease. Additionally, there are a number of clinical trials currently in process to evaluate several new agents that target RSV in the high-risk HSCT patient population.

Nguyen, T. M., A. Arthur, et al. "EphB4 Expressing Stromal Cells Exhibit an Enhanced Capacity for Hematopoietic Stem Cell Maintenance." Stem Cells. 2015 May 28. doi: 10.1002/stem.2069.

The tyrosine kinase receptor, EphB4, mediates cross-talk between stromal and hematopoietic populations during bone remodeling, fracture repair and arthritis, through its interactions with the ligand, ephrin-B2. This study demonstrated that transgenic EphB4 mice (EphB4 Tg), over-expressing EphB4 under the control of collagen type-1 promoter, exhibited higher frequencies of osteogenic cells and hematopoietic stem/progenitor cells (HSC), correlating with a higher frequency of long-term culture-initiating cells (LTC-IC), compared with wild type (WT) mice. EphB4 Tg stromal feeder layers displayed a greater capacity to support LTC-IC in vitro, where blocking EphB4/ephrin-B2 interactions decreased LTC-IC output. Similarly, short hairpin RNA-mediated EphB4 knockdown in human bone marrow stromal cells reduced their ability to support

high ephrin-B2 expressing CD34+ HSC in LTC-IC cultures. Notably, irradiated EphB4 Tg mouse recipients displayed enhanced bone marrow reconstitution capacity and enhanced homing efficiency of transplanted donor hematopoietic stem/progenitor cells relative to WT controls. Studies examining the expression of hematopoietic supportive factors produced by stromal cells indicated that CXCL12, Angiopoietin-1, IL-6, FLT-3 ligand, and osteopontin expression were more highly expressed in EphB4 Tg stromal cells compared with WT controls. These findings indicate that EphB4 facilitates stromal-mediated support of hematopoiesis, and constitute a novel component of the HSC niche. *Stem Cells* 2015.

Nishida, M., A. Shigematsu, et al. "Ultrasonographic evaluation of gastrointestinal graft-versus-host disease after hematopoietic stem cell transplantation." Clin Transplant. 2015 May 25. doi: 10.1111/ctr.12570.

Gastrointestinal graft-versus-host disease (GI-GVHD) is a major and life-threatening complication of hematopoietic stem cell transplantation (HSCT). This study evaluated the efficacy of ultrasonography (US) for assessing and monitoring GI-GVHD. GI tract was evaluated by US in 81 patients. US findings were positive in 43 patients, including 11 false positive, and negative in 38 patients. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of US for the diagnosis of GI-GVHD were 100%, 78%, 74%, 100% and 86%, respectively. Diffuse wall thickening of the ileum was the most frequent finding in GI-GVHD patients. Severity of GI-GVHD was correlated with the thickness of internal low echogenic layer of the wall, the echogenicity of mesenteric fat tissue, and the intensity of Doppler signaling. We classified US findings of GI-GVHD into 4 US grades. There was a significant correlation between clinical stage of GI-GVHD and the US grade. These ultrasonographic abnormalities were improved with clinical improvement of GI-GVHD upon treatment. Thus, US is an effective and efficient non-invasive means of identifying the extent and severity of GI-GVHD and monitoring response to treatment. This article is protected by copyright. All rights reserved.

Orchard, P. J., A. L. Fasth, et al. "Hematopoietic stem cell transplantation for infantile osteopetrosis." Blood. 2015 May 26. pii: blood-2015-01-625541.

We report the international experience in outcomes following related and unrelated hematopoietic transplantation for infantile osteopetrosis in 193 patients. Thirty-four percent of transplants used grafts from HLA-matched siblings, 13% from HLA-mismatched relatives, 12% from HLA-matched and 41% from HLA-mismatched

unrelated donors. The median age at transplantation was 12 months. Busulfan and cyclophosphamide was the most common conditioning regimen. Long-term survival was higher after HLA-matched sibling compared to alternative donor transplantation. There were no differences in survival after HLA-mismatched related, HLA-matched unrelated or mismatched unrelated donor transplantation. The 5- and 10-year probabilities of survival were 62% and 62% after HLA-matched sibling and 42% and 39% after alternative donor transplantation ( $p=0.01$  and  $p=0.002$  respectively). Graft failure was the most common cause of death accounting for 50% of deaths after HLA-matched sibling and 43% of deaths after alternative donor transplantation. The day-28 incidence of neutrophil recovery was 66% after HLA-matched sibling and 61% after alternative donor transplantation ( $p=0.49$ ). The median age of surviving patients is 7 years. Seventy percent of evaluable surviving patients are visually impaired and 10% have impaired hearing and gross motor delay. Nevertheless, 65% reported performance scores of 90 or 100, and in 17%, a score of 80 at last contact. Most survivors older than 5 years are attending mainstream or specialized schools. Rates of veno-occlusive disease and interstitial pneumonitis were high at 20%. Although allogeneic transplantation results in long-term survival with acceptable social function, strategies to lower graft failure and hepatic and pulmonary toxicity are urgently needed.

Otsu, K., M. Seki, et al. "Multiple myeloma recurring as small intestinal polyposis after autologous hematopoietic stem cell transplantation." *Rinsho Ketsueki*. 2015;56(4):400-5. doi: [10.11406/rinketsu.56.400](https://doi.org/10.11406/rinketsu.56.400).

A 52-year-old woman was diagnosed with BJP-lambda multiple myeloma (MM) in November 2012. She was treated with six cycles of bortezomib and dexamethasone, resulting in a very good partial response. The patient underwent autologous peripheral blood stem cell transplantation (PBSCT) 6 months after the diagnosis, and clearly achieved a complete response thereafter. She again suffered chronic abdominal pain with spontaneous remission 9 months after the PBSCT, and, 2 months thereafter, was hospitalized due to intestinal obstruction. Two small intestinal intussusceptions and polyposis in the small intestine were found on abdominal computed tomography. As conservative treatment produced no improvement, partial resection of the small intestine was performed. The pathologic review clearly demonstrated the polyps to have atypical plasma cell infiltrates in the mucosa of the small intestine involving all layers. Immunohisto-chemistry and FISH analyses yielded positive results for CD138, CD79a,

and lambda light chain, consistent with extramedullary relapse of MM. It is very rare for MM to present with polyposis in the small intestine. There have been no reports describing such a case after autologous PBSCT.

Paulson, K., S. G. Gilpin, et al. "Routine filtration of hematopoietic stem cell products: the time has arrived." *Transfusion*. 2015 May 18. doi: [10.1111/trf.13169](https://doi.org/10.1111/trf.13169).

**BACKGROUND:** Most blood products are infused at the time of transfusion through a standard blood filter, designed to capture macroaggregates and cellular debris that might be harmful to the patient if infused. Hematopoietic stem cell products are not universally filtered, likely due to concern about loss of viable stem cells in the filtration process. **STUDY DESIGN AND METHODS:** We conducted a two-phase study to better understand the safety of routine filtration. First, surplus cryopreserved stem cell products were thawed and filtered, with markers of viability and potency measured. Second, routine filtration was implemented as part of routine practice at our center, and date of neutrophil and platelet (PLT) recovery was compared to historical controls. **RESULTS:** In the first phase, there was no difference seen in any markers of viability or potency for products after routine filtration. Based on those results, routine filtration was implemented. There was no difference in neutrophil or PLT engraftment. Thus, in this study, routine filtration did not impact the number of viable stem cells and did not delay engraftment. **CONCLUSION:** Given the very real harm posed by infusion of macroaggregates and cellular debris, and no clear disadvantage to filtration, routine filtration of stem cell products should be considered the standard of care.

Pedrazzoli, P., M. Martino, et al. "High-Dose Chemotherapy With Autologous Hematopoietic Stem Cell Transplantation for High-Risk Primary Breast Cancer." *J Natl Cancer Inst Monogr*. 2015 May;2015(51):70-5. doi: [10.1093/jncimonographs/lgv010](https://doi.org/10.1093/jncimonographs/lgv010).

**BACKGROUND:** The efficacy of high-dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation for breast cancer (BC) has been an area of intense controversy among the medical oncology community. Over the last decade, due to the presentation of negative results from early randomized studies, this approach has not longer been considered an option by the vast majority of medical oncologists. This article is aimed to clarify what happened and where we are now in this not exhausted field. **METHODS:** We critically revised the published literature regarding HDC in the setting of high-risk

BC, including a recent meta-analysis using individual patient data from 15 randomized studies. RESULTS: A significant benefit by HDC in recurrence-free survival has been clearly documented in unselected patient populations. In HER2-negative population, particularly in the triple-negative disease, a positive effect of intensified therapy in overall survival is biologically plausible and supported by clinical evidence. Over the years HDC with support of adequate number of stem cells has become a safe treatment modality. CONCLUSIONS: The administration of higher doses of chemotherapy with stem cell support may still represent a therapeutic option (and not a recommendation) in selected BC patients. This approach should be investigated further.

Peffault de Latour, R., C. Peters, et al. "Recommendations on hematopoietic stem cell transplantation for inherited bone marrow failure syndromes." *Bone Marrow Transplant*. 2015 Jun 8. doi: 10.1038/bmt.2015.117.

Allogeneic hematopoietic stem cell transplantation (HSCT) offers the potential to cure patients with an inherited bone marrow failure syndrome (IBMFS). However, the procedure involves the risk of treatment-related mortality and may be associated with significant early and late morbidity. For these reasons, the benefits should be carefully weighed against the risks. IBMFS are rare, whereas case reports and small series in the literature illustrate highly heterogeneous practices in terms of indications for HSCT, timing, stem cell source and conditioning regimens. A consensus meeting was therefore held in Vienna in September 2012 on behalf of the European Group for Blood and Marrow Transplantation to discuss HSCT in the setting of IBMFS. This report summarizes the recommendations from this expert panel, including indications for HSCT, timing, stem cell source and conditioning regimen. *Bone Marrow Transplantation advance online publication*, 8 June 2015; doi:10.1038/bmt.2015.117.

Peters, S. G. "Is bronchiolitis obliterans after hematopoietic stem cell transplantation reversible?" *Am J Respir Crit Care Med*. 2015 Jun 1;191(11):1214-6. doi: 10.1164/rccm.201504-0720ED.

Pigneux, A., M. Labopin, et al. "Outcome of allogeneic hematopoietic stem-cell transplantation for adult patients with AML and 11q23/MLL rearrangement (MLL-r AML)." *Leukemia*. 2015 Jun 17. doi: 10.1038/leu.2015.143.

Acute myeloid leukemia (AML) with 11q23/MLL rearrangement (MLL-r AML) is allocated to the intermediate or high-risk cytogenetic prognostic

category depending on the MLL fusion partner. A more favourable outcome has been reported in patients receiving an allogeneic hematopoietic stem-cell transplantation (alloHSCT), but this has not been confirmed in large series. We analyzed the outcome of alloHSCT among adult patients reported to the ALWP between 2000 and 2010. We identified 159 patients with 11q23/MLL rearranged AML allografted in first complete remission (CR1, n=138) or CR2, mostly corresponding to t(9;11), t(11;19), t(6;11), and t(10;11) translocations. Two-year overall survival (OS), leukemia-free survival (LFS), relapse incidence (RI), and non-relapse mortality (NRM) was 56+/-4%, 51+/-4%, 31+/-3%, and 17+/-4%, respectively. The outcome differed according to 11q23/MLL rearrangement, being more favourable in patients with t(9;11) and t(11;19) compared to t(10;11) and t(6;11) (2-year OS: 64+/-6% and 73+/-10% vs 40+/-13% and 24+/-11%, respectively; P<0.0001). Multivariate analysis for OS identified t(6;11), t(10;11), age>40 years and CR2 as unfavourable features, whereas t(6;11), t(10;11), CR2 and the use of RIC regimen affected poorly LFS. This study confirms the potential role of alloHSCT for adult patients with 11q23/MLL rearranged AML in CR1. *Leukemia accepted article preview online*, 17 June 2015. doi:10.1038/leu.2015.143.

Pilie, P., W. A. Werbel, et al. "Adult patients with respiratory syncytial virus infection: impact of solid organ and hematopoietic stem cell transplantation on outcomes." *Transpl Infect Dis*. 2015 Jun 8. doi: 10.1111/tid.12409.

BACKGROUND: Respiratory syncytial virus (RSV) is a common community-acquired pathogen responsible for a substantial disease burden in adults. We investigated outcomes after RSV infection in hospitalized adults over a 3-year period. METHODS: This single-center, retrospective study identified 174 patients hospitalized with RSV upper or lower respiratory tract infection (LRTI) between January 1, 2009 and June 30, 2012. Clinical data were extracted from medical records. The primary outcome analyzed was all-cause mortality, defined as death during the index hospital admission. Subjects were divided into 3 groups for comparison: hematopoietic stem cell transplant (HSCT) patients, solid organ transplant (SOT) patients, and non-transplant patients. RESULTS: In our study, 41/174 (23.6%) were HSCT recipients and 28/174 (16.1%) were SOT recipients. Twelve of 174 (6.9%) died. Death occurred in 2/41 (4.9%) HSCT and 3/28 (10.7%) SOT recipients, compared to 7/106 (6.6%) of non-transplant patients. When compared to the non-transplant cohort, HSCT and SOT were not found to be significant risk factors for mortality (P = 0.685 and P = 0.645, respectively).

In multivariate logistic regression, age >60 was associated with mortality ( $P = 0.019$ ), while lymphopenia on admission trended towards an association with death ( $P = 0.054$ ). HSCT patients were less likely to be admitted to an intensive care unit (odds ratio [OR] 0.26,  $P = 0.04$ ), but were significantly more likely to receive ribavirin therapy (OR 11.62,  $P < 0.0001$ ). CONCLUSIONS: Adults hospitalized with RSV LRTI are at significant risk of mortality, and this risk may be increased in patients age >60 or with lymphopenia on admission. This study did not identify any significant increased mortality or morbidity associated with RSV infection in immune suppressed transplant recipients vs. patients who had not received a transplant. This article is protected by copyright. All rights reserved.

Rabenhorst, U., F. B. Thalheimer, et al. "Single-Stranded DNA-Binding Transcriptional Regulator FUBP1 Is Essential for Fetal and Adult Hematopoietic Stem Cell Self-Renewal." *Cell Rep.* 2015 Jun 17. pii: S2211-1247(15)00574-4. doi: 10.1016/j.celrep.2015.05.038.

The ability of hematopoietic stem cells (HSCs) to self-renew is a prerequisite for the establishment of definitive hematopoiesis and life-long blood regeneration. Here, we report the single-stranded DNA-binding transcriptional regulator far upstream element (FUSE)-binding protein 1 (FUBP1) as an essential factor of HSC self-renewal. Functional inactivation of FUBP1 in two different mouse models resulted in embryonic lethal anemia at around E15.5 caused by severely diminished HSCs. Fetal and adult HSCs lacking FUBP1 revealed an HSC-intrinsic defect in their maintenance, expansion, and long-term blood reconstitution, but could differentiate into all hematopoietic lineages. FUBP1-deficient adult HSCs exhibit significant transcriptional changes, including upregulation of the cell-cycle inhibitor p21 and the pro-apoptotic Noxa molecule. These changes caused an increase in generation time and death of HSCs as determined by video-microscopy-based tracking. Our data establish FUBP1 and its recognition of single-stranded genomic DNA as an important element in the transcriptional regulation of HSC self-renewal.

Reisner, Y., F. Aversa, et al. "Haploidentical hematopoietic stem cell transplantation: state of art." *Bone Marrow Transplant.* 2015 Jun;50 Suppl 2:S1-5. doi: 10.1038/bmt.2015.86.

For patients with hematologic malignancies at high risk of relapse who do not have matched donors, a suitable alternative stem cell source is the HLA-haploidentical 2- or 3-loci mismatched family donor who is readily available for nearly all patients. Transplantation across the major HLA barrier is

associated with strong T-cell alloreactions, which were originally manifested as a high incidence of severe GVHD and graft rejection. The present overview of the 7th symposium on haploidentical transplantation that took place at the Weizmann Institute on February 2014, shows how these obstacles to successful transplantation can now be overcome. The review also discusses the advantages and drawbacks of current options for full haplotype-mismatched transplantation and highlights innovative approaches for rebuilding immunity, reducing leukemia relapse and improving survival after transplantation. In addition, new modalities for immune tolerance induction following nonmyeloablative conditioning are discussed, showing new options for treatment of elderly patients who cannot tolerate myeloablative conditioning protocols, as well as novel strategies for immune tolerance and chimerism induction as a platform for cell therapy and organ transplantation.

Rouso, S. Z., O. Shamriz, et al. "Hematopoietic Stem Cell Transplantations for Primary Immune Deficiencies: 3 Decades of Experience From a Tertiary Medical Center." *J Pediatr Hematol Oncol.* 2015 Jul;37(5):e295-300. doi: 10.1097/MPH.0000000000000352.

Hematopoietic stem cell transplantation (HSCT) remains the leading treatment for the majority of severe primary immune deficiency (PID). This study aims to analyze changes in outcome over time. We conducted a retrospective analysis of HSCT in children with PID in a tertiary medical center over the period of 1983 to 2012. We identified 93 children with PID with a median follow-up of 3.6 years (range, 29 d to 21.2 y) after HSCT. The 2-year survival rates after HSCT for children with severe combined immune deficiency, hemophagocytic lymphohistiocytosis/lymphoproliferative disease, Wiskott-Aldrich syndrome, granulocyte defect, and undefined PID were 65.7%±6.8%, 80%±10.3%, 83.3%±15.2%, 75%±12.5%, and 25%±21.7%, respectively. Survival was associated with year of HSCT and matching. The hazard ratio (HR) (95% CI) for HSCT done in 1983 to 1999 compared with 2000 to 2012 and for matched (related and unrelated) compared with mismatched donor were 2.14 (0.99 to 4.653) and 3.07 (1.46 to 6.4), respectively. Survival was not associated with age, sex of the recipient, underlying PID, conditioning regimen, and presence of acute graft-versus-host disease. After adjustment to the underlying PID, donor and use of fludarabine-based conditioning, the HR (95% CI) for HSCT from the year 2000 was 4.69 (range, 1.4 to 15.45). Advances in HSCT over time have improved the survival of children with PID.

Rundberg Nilsson, A., C. J. Pronk, et al. "Probing hematopoietic stem cell function using serial transplantation: Seeding characteristics and the impact of stem cell purification." *Exp Hematol.* 2015 May 29. pii: [S0301-472X\(15\)00169-1](#). doi: [10.1016/j.exphem.2015.05.003](#).

Appropriate regulation of hematopoietic stem cell (HSC) numbers and function is a requisite for life-long blood cell replenishment. Knowledge of factors that regulate HSC activity is derived largely from murine model systems, with serial transplantation often considered a "gold standard" to assess longevity and self-renewal of HSCs. In the literature, we noted inconsistencies in how serial transplantations are conducted and decided to assess a set of parameters at play in such experiments. We found that HSCs distribute and expand unevenly among individual bones following transplantation, suggesting that isolation of a limited number of bone marrow cells for serial transplantation and/or analysis can influence experimental outcomes. Comparing donor cell output from transplanted unfractionated bone marrow cells, as opposed to fluorescence-activated cell-sorted HSCs, revealed distinct differences in the output of mature blood cells. Specifically, we found that long-lived progenitor and/or mature co-transplanted cells can severely affect the interpretation of ongoing HSC activity in secondary hosts. The implications of these data for the design and execution of serial transplantation experiments are discussed.

Ruzhansky, K. M. and T. H. Brannagan, 3rd "Neuromuscular complications of hematopoietic stem cell transplantation." *Muscle Nerve.* 2015 Jun 4. doi: [10.1002/mus.24724](#).

Neuromuscular complications such as polymyositis, dermatomyositis, neuropathy, and disorders of neuromuscular transmission are reported to be complications of hematopoietic stem cell transplantation (HSCT). Although cases have been reported with allogeneic HSCT in the setting of chronic graft versus host disease, they are also known to occur without evidence thereof and even occur in the setting of autologous HSCT. The 2005 NIH Consensus Criteria classify polymyositis and dermatomyositis as 'distinctive' features, and neuropathy and MG as "other" features. These neuromuscular complications present very similarly to the idiopathic autoimmune disorders and respond to similar treatment modalities. This article is protected by copyright. All rights reserved.

Sato, K., M. Sumi, et al. "Chromosomally integrated human herpesvirus-6 requiring differential diagnosis of reactivation after allogeneic hematopoietic stem

cell transplantation." *Rinsho Ketsueki.* 2015;56(4):406-11. doi: [10.11406/rinketsu.56.406](#).

Human herpesvirus-6 (HHV-6) is known to cause critical encephalitis, as a central nervous system infection, in some hematopoietic stem cell transplantation (HSCT) recipients. Chromosomally integrated human herpesvirus-6 (CIHHV-6) persistently shows HHV-6 DNA in blood, but this does not necessarily suggest active infection. The true clinical significance in HSCT is not clear. The prevalence of CIHHV-6 in Japan is reportedly 0.21%. We herein report two HSCTs: from a CIHHV-6-positive donor to a negative recipient and from a negative donor to a positive recipient. In the CIHHV-6-positive donor case, the recipient's plasma, which had been negative for HHV-6 before HSCT, became positive after transplantation and the level then remained high, although the subject was asymptomatic. In the CIHHV-6-positive recipient case, the patient's plasma viral load was high just after transplantation, although the subject was asymptomatic, and the load gradually decreased after engraftment. Antivirals had no effect on the viral load in either case. We should consider CIHHV-6 when the HHV-6 DNA load in blood persists asymptotically after HSCT, to avoid misdiagnosis of reactivated HHV-6 infection and overuse of antivirals. It is also useful to monitor HHV-6 DNA in blood before HSCT, to distinguish HHV-6 reactivation from CIHHV-6.

Schargus, M., T. Meyer-Ter-Vehn, et al. "Correlation Between Tear Film Osmolarity and the Disease Score of the International Chronic Ocular Graft-Versus-Host-Disease Consensus Group in Hematopoietic Stem Cell Transplantation Patients." *Cornea.* 2015 Jun 10.

**PURPOSE:** To evaluate tear film osmolarity (TFO) as a diagnostic tool for detecting chronic ocular graft-versus-host disease (GVHD) in patients after hematopoietic stem cell transplantation and to assess its correlation with the new international chronic ocular GVHD score. **METHODS:** A group of 204 consecutive patients who underwent hematopoietic stem cell transplantation at University Hospital Wuerzburg in Germany received an ophthalmologic examination after transplantation. TFO was measured and the chronic ocular GVHD score was calculated based on the Schirmer test, corneal fluorescein staining, conjunctival injection, Ocular Surface Disease Index questionnaire, and presence of systemic GVHD. **RESULTS:** A total of 172 patients showed no chronic ocular GVHD. Of the remaining 32 patients using the international chronic ocular GVHD score, 21 were classified as "probably" and 11 as "definite" chronic ocular GVHD. TFO was positively correlated

with the new chronic ocular GVHD score ( $P < 0.01$ ,  $r = 0.35$ ). TFO differed significantly between patients with no ocular GVHD ( $300 \pm 16.5$  mOsm/L) and definite ocular GVHD ( $337 \pm 36$  mOsm/L)-a receiver operating characteristic analysis showed high discrimination capability (area under the curve:  $0.91 \pm 0.04$ ) and suggested a threshold level of the TFO value of 312 mOsm/L yielding a sensitivity of 91% and a specificity of 82%. CONCLUSIONS: TFO can be used for detecting chronic ocular GVHD with high sensitivity and specificity as a noninvasive objective test in addition to traditional dry eye tests. It correlates positively with the diagnostic criteria of a recently established international consensus score for diagnosing the disease.

Schlegel, P., T. Feuchtinger, et al. "Favorable NK cell activity after haploidentical hematopoietic stem cell transplantation in stage IV relapsed Ewing's sarcoma patients." Bone Marrow Transplant. 2015 Jun;50 Suppl 2:S72-6. doi: 10.1038/bmt.2015.100.

Natural killer (NK) cell activity has been shown to have potential activity against Ewing's sarcoma (EWS) especially in tumors with low HLA I expression and high NKG2D expression. Two patients with metastatic relapsed and primary metastatic stage IV EWS who had received two courses of high dose chemotherapy with autologous stem cell rescue were transplanted from a haploidentical parental stem cell donor. Patients are alive in ongoing CR for 10.2 and 3.4 years now. Post transplant local second and first relapses were treated successfully in both patients. In vivo IL-2 stimulation not only increased the number and activity of effector cells in one patient but was also associated with severe GvHD. In vitro studies demonstrated high NK cell activity against K562 and relevant activity against EWS cell line A673 post transplant. NK activity was enhanced by cytokine prestimulation as well as by EWS targeting anti-GD2 Ab. Haploidentical hematopoietic stem cell transplantation (HSCT) might contribute to long-term survival by NK cell-mediated effect exerted by donor-derived NK cells. Local tumor recurrence was manageable in both high-risk patients indicating systemic immune control preventing subsequent metastasizing. The efficacy of haploidentical HSCT, cytokine application and tumor targeting antibodies for the use of Ab-dependent cellular cytotoxicity needs evaluation in clinical trials.

Sestier, B. "[Hematopoietic stem cell exhaustion and advanced glycation end-products in the unexplained anemia of the elderly]." Rev Esp Geriatr Gerontol. 2015 Jun 19. pii: S0211-139X(15)00041-4. doi: 10.1016/j.regg.2015.03.006.

INTRODUCTION: More than 10% of the aged 65 years and over in the western world suffers anemia and in one third of them the cause of the anemia remains obscure. The unexplained anemia of the elderly (UAE) is considered an exclusion diagnosis, without the existence of a clear consensus to its clinical or experimental approach. There is an association between aging and anemia in studies performed in animals and in humans. OBJECTIVES: To determine if there is evidence in the literature that supports hematopoietic stem cells (HSC) exhaustion and the advanced glycation end-products (AGE's) as a cause of UAE. METHOD: A total of 32 combined texts (28 for HSC exhaustion and 4 for AGEs) were selected after an intensive review. Conclusions were associated with causes and effects of the HSC exhaustion and circulating AGE's over aging and anemia. RESULTS: Only three works try to establish an association between UAE and HSC exhaustion, two of them disagreed in their conclusions, with the third one differing in the type of study. There is a relationship between anemia and AGEs increase and accumulation. CONCLUSIONS: There is evidence in the literature that links the aging molecular and cellular mechanisms with the HSC exhaustion and the increase of AGE's. Furthermore; there is some evidence that both conditions determine the emergence of anemia associated with age in animals and in humans. There is little evidence in the literature to clarify the relationship between aging and UAE.

Shah, G. L., A. Winn, et al. "Cost-Effectiveness of Autologous Hematopoietic Stem Cell Transplantation for Elderly Patients with Multiple Myeloma using the Surveillance, Epidemiology, and End Results-Medicare Database." Biol Blood Marrow Transplant. 2015 May 30. pii: S1083-8791(15)00336-5. doi: 10.1016/j.bbmt.2015.05.013.

In the past decade, the number of autologous hematopoietic stem cell transplants (Auto HSCT) for older patients with multiple myeloma (MM) has increased dramatically, as has the cost of transplantation. The cost-effectiveness of this modality in patients over age 65 is unclear. Using the Surveillance, Epidemiology, and End Results-Medicare database to create a propensity-score matched sample of patients over age 65 between 2000 and 2007, we compared the survival and cost for those who received Auto HSCT to those who did not undergo transplantation but survived at least 6 months after diagnosis, and we calculated an incremental cost-effectiveness ratio (ICER). Two hundred seventy patients underwent transplantation. Median overall survival from diagnosis in those who underwent transplantation was significantly longer than in patients who did not (58 months versus 37 months, P

< .001). For patients living longer than 2 years, the median monthly cost during the first year was significantly different, but the middle and last year of life costs were similar. The median cost of the first 100 days after transplantation was \$60,000 (range, \$37,000 to \$85,000). The resultant ICER was \$72,852 per life-year gained. Survival after transplantation was comparable to that in those who underwent transplantation patients under 65 years and significantly longer than older patients who did not undergo transplantation. With an ICER less than \$100,000/life-year gained, Auto HSCT is cost-effective when compared with nontransplantation care in the era of novel agents and should be considered, where clinically indicated, for patients over the age of 65.

Sobiak, J., U. Kazimierzak, et al. "Clinical and In Vitro Studies on Impact of High-Dose Etoposide Pharmacokinetics Prior Allogeneic Hematopoietic Stem Cell Transplantation for Childhood Acute Lymphoblastic Leukemia on the Risk of Post-Transplant Leukemia Relapse." Arch Immunol Ther Exp (Warsz). 2015 Jun 4.

The impact of etoposide (VP-16) plasma concentrations on the day of allogeneic hematopoietic stem cell transplantation (allo-HSCT) on leukemia-free survival in children with acute lymphoblastic leukemia (ALL) was studied. In addition, the in vitro effects of VP-16 on the lymphocytes proliferation, cytotoxic activity and on Th1/Th2 cytokine responses were assessed. In 31 children undergoing allo-HSCT, VP-16 plasma concentrations were determined up to 120 h after the infusion using the HPLC-UV method. For mentioned in vitro studies, VP-16 plasma concentrations observed on allo-HSCT day were used. In 84 % of children, VP-16 plasma concentrations (0.1-1.5 mug/mL) were quantifiable 72 h after the end of the drug infusion, i.e. when allo-HSCT should be performed. In 20 (65 %) children allo-HSCT was performed 4 days after the end of the drug infusion, and VP-16 was still detectable (0.1-0.9 mug/mL) in plasma of 12 (39 %) of them. Post-transplant ALL relapse occurred in four children, in all of them VP-16 was detectable in plasma (0.1-0.8 mug/mL) on allo-HSCT day, while there was no relapse in children with undetectable VP-16. In in vitro studies, VP-16 demonstrated impact on the proliferation activity of stimulated lymphocytes depending on its concentration and exposition time. The presence of VP-16 in plasma on allo-HSCT day may demonstrate an adverse effect on graft-versus-leukemia (GvL) reaction and increase the risk of post-transplant ALL relapse. Therefore, if 72 h after VP-16 administration its plasma concentration is still above 0.1 mug/mL then the postponement of transplantation for next 24 h

should be considered to protect GvL effector cells from transplant material.

Tischer, J., N. Engel, et al. "Virus infection in HLA-haploidentical hematopoietic stem cell transplantation: incidence in the context of immune recovery in two different transplantation settings." Ann Hematol. 2015 Jun 10.

We retrospectively compared the incidence of virus infections and outcome in the context of immune reconstitution in two different HLA-haploidentical transplantation (haplo-HSCT) settings. The first was a combined T-cell-replete and T-cell-deplete approach using antithymocyte globulin (ATG) prior to transplantation in patients with hematological diseases (cTCR/TCD group, 28 patients; median age 31 years). The second was a T-cell-replete (TCR) approach using high-dose posttransplantation cyclophosphamide (TCR/PTCY group, 27 patients; median age 43 years). The incidence of herpesvirus infection was markedly lower in the TCR/PTCY (22 %) than in the cTCR/TCD group (93 %). Recovery of CD4+ T cells on day +100 was faster in the TCR/PTCY group. CMV reactivation was 30 % in the TCR/PTCY compared to 57 % in the cTCR/TCD group, and control with antiviral treatment was superior after TCR/PTCY transplantation (100 vs 50 % cTCR/TCD). Twenty-five percent of the patients in the cTCR/TCD group but no patient in the TCR/PTCY group developed PTLD. While 1-year OS was not different (TCR/PTCY 59 % vs cTCR/TCD 39 %; p = 0.28), virus infection-related mortality (VIRM) was significantly lower after TCR/PTCY transplantation (1-year VIRM, 0 % TCR/PTCY vs 29 % cTCR/TCD; p = 0.009). On day +100, predictors of better OS were lymphocytes >300/mul, CD3+ T cells >200/mul, and CD4+ T cells >150/mul, whereas the application of steroids >1 mg/kg was correlated with worse outcome. Our results suggest that by presumably preserving antiviral immunity and allowing fast immune recovery of CD4+ T cells, the TCR approach using posttransplantation cyclophosphamide is well suited to handle the important issue of herpesvirus infection after haplo-HSCT.

Wallace, G., S. Jodele, et al. "Vitamin D Deficiency and Survival in Children after Hematopoietic Stem Cell Transplant." Biol Blood Marrow Transplant. 2015 Jun 17. pii: S1083-8791(15)00411-5. doi: 10.1016/j.bbmt.2015.06.009.

Vitamin D has endocrine function as a key regulator of calcium absorption and bone homeostasis, and also has intracrine function as an immunomodulator. Vitamin D deficiency prior to HSCT has been variably associated with a higher risk

of GVHD, and of mortality. Children are at particular risk of growth impairment and bony abnormalities in the face of prolonged deficiency. There are few longitudinal studies of vitamin D children receiving HSCT, and the prevalence and consequences of vitamin D deficiency 100 days after transplant has been poorly studied. Serum samples from 134 consecutive HSCT patients prospectively enrolled into an HSCT sample repository were tested for 25-hydroxy (25 OH) vitamin D levels prior to starting HSCT (baseline) and at 100 days after transplantation. Ninety-four of 134 (70%) of patients had a vitamin D level < 30 ng/ml prior to HSCT, despite supplemental therapy in 16% of subjects. Post-transplant samples were available in 129 patients who survived to day 100 post transplant. Vitamin D deficiency persisted in 66 of 87 patients (76%) who were already deficient prior to HSCT. Moreover, twenty-four patients with normal vitamin D levels prior to HSCT were vitamin D deficient by day 100. Overall, 68% of patients were vitamin D deficient (< 30ng/ml) at day 100, and one third of these cases had severe vitamin D deficiency (< 20 ng/ml). Low vitamin D levels prior to HSCT were not associated with subsequent acute or chronic GVHD, contrary to some prior reports. However, severe vitamin D deficiency (< 20 ng/ml) at 100 days post-HSCT was associated with decreased overall survival after transplantation (p=0.044, 1-year OS 70% vs. 84.1%). We conclude that all pediatric transplant recipients should be screened for vitamin D deficiency prior to HSCT, and at day 100 post-transplant, and that aggressive supplementation is needed to maintain sufficient levels.

Yew, P. Y., H. Alachkar, et al. "Quantitative characterization of T-cell repertoire in allogeneic hematopoietic stem cell transplant recipients." Bone Marrow Transplant. 2015 Jun 8. doi: [10.1038/bmt.2015.133](https://doi.org/10.1038/bmt.2015.133).

Allogeneic hematopoietic stem cell transplantation (HSCT) is one of curative treatment options for patients with hematologic malignancies. Although GVHD mediated by the donor's T lymphocytes remains the most challenging toxicity of allo-HSCT, graft-versus-leukemia (GVL) effect targeting leukemic cells, has an important role in affecting the overall outcome of patients with AML. Here we comprehensively characterized the TCR repertoire in patients who underwent matched donor or haplo-cord HSCT using next-generation sequencing approach. Our study defines the functional kinetics of each TCRA and TCRB clone, and changes in T-cell diversity (with identification of CDR3 sequences) and the extent of clonal expansion of certain T-cells. Using this approach, our study demonstrates that higher percentage of cord-blood cells at 30 days after

transplant was correlated with higher diversity of TCR repertoire, implicating the role of cord-chimerism in enhancing immune recovery. Importantly, we found that GVHD and relapse, exclusive of each other, were correlated with lower TCR repertoire diversity and expansion of certain T-cell clones. Our results highlight novel insights into the balance between GVHD and GVL effect, suggesting that higher diversity early after transplant possibly implies lower risks of both GVHD and relapse following the HSCT transplantation. Bone Marrow Transplantation advance online publication, 8 June 2015; doi:10.1038/bmt.2015.133.

Yoo, J. J., E. J. Cho, et al. "Efficacy of antiviral prophylaxis in HBsAg-negative, anti-HBc positive patients undergoing hematopoietic stem cell transplantation." Liver Int. 2015 Jun 3. doi: [10.1111/liv.12882](https://doi.org/10.1111/liv.12882).

**BACKGROUND & AIMS:** Hepatitis B virus (HBV) reactivation can occur in persons who are hepatitis B surface antigen (HBsAg)-negative but hepatitis B core antibody (anti-HBc) positive, especially following hematopoietic stem cell transplantation (HSCT). However, evidence supporting the routine use of prophylactic antiviral agents for such patients is scarce. The aim of this study was to compare the frequency of HBV reactivation between prophylactic and non-prophylactic groups in patients who underwent HSCT. **METHODS:** This retrospective cohort study included 315 HBsAg-negative, anti-HBc positive patients who received autologous or allogeneic stem cell transplantation from January 2008 to December 2013. Patients were categorized into prophylactic and non-prophylactic groups. The primary endpoint was the incidence of HBV reactivation. **RESULTS:** Median follow-up duration was 21.4 months. Antiviral prophylaxis was not given to 219 patients, and 96 received prophylaxis. The median duration of prophylaxis was 7.0 months. HBV reactivated in 12 patients (prophylactic group, 4; non-prophylactic group, 8). The median time to reactivation was 20.5 months after starting chemotherapy. All patients who reactivated were promptly and successfully treated with rescue antiviral agents. The risk of reactivation did not differ between prophylactic and non-prophylactic groups (P = 0.061) but was increased significantly by the allogeneic type of HSCT and the loss of recipient's antibodies against HBsAg (anti-HBs). **CONCLUSIONS:** Short-term antiviral prophylaxis appears insufficient to decrease the risk of HBV reactivation. Therefore, either prophylaxis longer than 24 months or careful monitoring of HBV DNA combined with on-demand antiviral treatment

may prove more effective than the routine short-term prophylaxis given to these patients.

Zoller, M. "CD44, Hyaluronan, the Hematopoietic Stem Cell, and Leukemia-Initiating Cells." Front Immunol. 2015 May 26;6:235. doi: 10.3389/fimmu.2015.00235. eCollection 2015.

CD44 is an adhesion molecule that varies in size due to glycosylation and insertion of so-called variant exon products. The CD44 standard isoform (CD44s) is highly expressed in many cells and most abundantly in cells of the hematopoietic system, whereas expression of CD44 variant isoforms (CD44v) is more restricted. CD44s and CD44v are known as stem cell markers, first described for hematopoietic stem cells and later on confirmed for cancer- and leukemia-initiating cells. Importantly, both abundantly expressed CD44s as well as CD44v actively contribute to the maintenance of stem cell features, like generating and embedding in a niche, homing into the niche, maintenance of quiescence, and relative apoptosis resistance. This is surprising, as CD44 is not a master stem cell gene. I here will discuss that the functional contribution of CD44 relies on its particular communication skills with neighboring molecules, adjacent cells and, last not least, the surrounding matrix. In fact, it is the interaction of the hyaluronan receptor CD44 with its prime ligand, which strongly assists stem cells to fulfill their special and demanding tasks. Recent fundamental progress in support of this "old" hypothesis, which may soon pave the way for most promising new therapeutics, is presented for both hematopoietic stem cell and leukemia-initiating cell. The contribution of CD44 to the generation of a stem cell niche, to homing of stem cells in their niche, to stem cell quiescence and apoptosis resistance will be in focus.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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