Literature summaries are provided as information only. Please refer to the original published articles for complete details on study methodology, results and discussion.

*** Must read. Landmark publication that affects practice
** Recommend reading. Secondary paper that adds to literature
* Consider reading. Cursory importance to the practice

Hematopoietic Cell Transplantation

**Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol.* 2017 Feb 13 [Epub ahead of print]

- Randomized, multicenter phase III trial comparing MAC (n=135) versus RIC (n=137) followed by HCT from MRD or MUD in adult patients with AML or MDS.
- Accrual ended early due to significantly higher relapse at 18 months with RIC (48.3%; 95% CI, 39.6% to 56.4%) versus MAC (13.5%; 95% CI, 8.3% to 19.8%) (*P*<.001); relapse was the primary cause of death (86.4%) for those receiving RIC.
- TRM at 18 months was significantly higher in the MAC arm (15.8%; 95% CI, 10.2% to 22.5%) versus the RIC arm (4.4%; 95% CI, 1.8% to 8.9%) (*P*=.002); GVHD was the primary cause of death (50%) for those receiving MAC.
- The primary endpoint of OS at 18 months post-random assignment was 77.5% (95% CI, 69.4% to 83.7%) in the MAC arm and 67.7% (95% CI, 59.1% to 74.9%) in the RIC arm (*P*=.07); this was not statistically significant.
- When treating death and relapse as competing risks, the cumulative incidence of grade 2-4 GVHD at day 100 was 44.7% (95% CI, 36% to 53%) with MAC and 28.6% (95% CI, 21% to 36%) with RIC (*P*=.006); grade 3-4 GVHD at day 100 was 14.4% (95% CI, 9% to 21%) with MAC and 3.8% (95% CI, 1% to 8%) with RIC (*P*=.003); chronic GVHD at 18 months was 65.6% (95% CI, 57% to 73%) with MAC and 36.9% (95% CI, 28% to 45%) with RIC (*P*<.01).
- The authors concluded that although RIC lowered TRM, this benefit was offset by significantly higher relapse rates in those receiving MAC. Even though the difference in OS was not statistically significant, OS was numerically lower for those receiving RIC. The data supports the use of MAC as standard of care for fit patients with AML or MDS.

*Purev E, Tian X, Aue G, et al. Allogeneic transplantation using CD34+ selected peripheral blood progenitor cells combined with non-mobilized donor T cells for refractory severe aplastic anemia. *Br J Haematol*. 2017 Feb 7. Doi: 10.1111/bjh.14448. [Epub ahead of print]
https://www.ncbi.nlm.nih.gov/pubmed/28169418

- Prospective, non-randomized study of 15 heavily-transfused patients with bone marrow failure syndromes (BMFS) who underwent MRD HCT with GCSF-mobilized T-cell depleted CD34+ cells co-infused with a HCT equivalent dose of non-mobilized donor T-cells. Outcomes were compared with a historical cohort of 56 similar patients who received unmanipulated PBSC transplant.
- All patients in the study cohort achieved neutrophil recovery occurring at a median time of 14 days (range 10-23), 14/15 (93%) achieved platelet recovery at a median time of 18 days (range 9-321), and none experienced graft rejection. Results were similar in both cohorts.
- All patients in the study cohort achieved full donor (≥95%) T-cell and myeloid chimerisms at a median time of 30 days (range 15-730) and 15 days (range 15-30) post-transplant, respectively. Although myeloid engraftment was similar to the historical cohort, the study cohort was significantly slower in achieving full-donor T-cell chimerism (53% vs 82% by day 30; *P*=0.014).
- Two patients each (13%) developed acute grade II-IV (95% CI: 2-35) and chronic GVHD (95% CI: 2-35) in the study cohort at day 100. The historical cohort experienced significantly more grade II-IV aGVHD (13% vs 52%; *P*=0.010) and cGVHD (13% vs 72%; *P*=0.0004).
- With a median follow-up of 42 months (range 11-61), 13 out of 15 patients in the study cohort survived, for an estimated OS probability of 86% (95% CI: 71-100). OS was comparable between cohorts (86% vs 87%; *P*=0.86).
- Although this method showed delayed T-cell reconstitution, the authors concluded that this method achieves excellent engraftment and survival with a reduction in acute and cGVHD without increasing the risk of graft rejection. These findings are hypothesis-generating and warrant further investigation especially among lower-risk severe aplastic anemia patients with treatment-naïve disease.

**Castagna L, Bramanti S, Devillier R, et al. Haploidentical transplantation with post-infusion cyclophosphamide in advanced Hodgkin lymphoma. *Bone Marrow Transplant*. 2017 Jan 16. DOI:10.1038/bmt.2016.348.
https://www.ncbi.nlm.nih.gov/pubmed/28092347

- Prospective study included 62 patients with relapsed HL without a HLA identical donor who received a haploidentical transplant with post-transplant cyclophosphamide.
- Eighty-seven percent of patients were in CR or PR prior to their haplo-HCT. Eighty-five percent of patients had received prior high dose chemotherapy, and 10% had a prior alloHCT.
- Median time to neutrophil engraftment was 20 days. Two patients experienced graft failure due to donor-specific antibodies.
- Incidence of grades II-IV aGVHD was 23% at 100 days. Sixteen percent of patients experienced cGVHD.
- 3-year OS and PFS were 63% and 59%, respectively. Overall 1 year NRM was 20%, but found to be 11% in patients receiving a NMA conditioning regimen. The relapse rate was 21%.
- The authors concluded that using haplo-HCT with post-transplant cyclophosphamide in patients with relapsed HL without a matched donor is a good option, particularly for those who achieve PR or CR prior to haplo-HCT.

*Mallhi K, Orchard PJ, Miller WP, et al. Non-myeloablative conditioning for second hematopoietic cell transplantation for graft failure in patients with non-malignant disorders: a prospective study and review of the literature. *Bone Marrow Transplant*. 2017 Jan 16. DOI:10.1038/bmt.2016.356. [Epub ahead of print]
https://www.ncbi.nlm.nih.gov/pubmed/28092353

- Single-center study evaluating 17 children with non-malignant disorders undergoing a second allogeneic transplant for graft failure, all receiving NMA conditioning with low dose TBI, low dose busulfan and fludarabine.
- 12 patients had received RIC with their first transplant, and 13 received a cord blood source.
- Median time to second transplant was 85 days.
- Stable donor hematopoiesis was achieved in 88% of patients; 82% patients achieved neutrophil recovery by day 42, while 3 patients experienced neutropenic graft failure.
- 3-year OS was 82%. TRM at day 100 was 12%.
- Incidence of grades II-IV aGVHD was 35% at day 180, while the incidence of cGVHD was 19%.
- The authors concluded that a second transplant with NMA conditioning is a potential option for patients experiencing graft failure after a HCT for a non-malignant disorder, as they have reported a good OS with minimal TRM.

GVHD Prophylaxis/Treatment

*Socié G, Vigouroux S, Yakoub-Agha I, et al. A phase 3 randomized trial comparing inolimomab vs usual care in steroid-resistant acute GVHD. *Blood.* 2017;129:643-649.
https://www.ncbi.nlm.nih.gov/pubmed/27899357

- Phase III trial that randomized 100 adult alloHCT patients with steroid-resistant aGVHD to inolimomab (monoclonal antibody against the interleukin-2 receptor) vs usual care (rabbit ATG)
- Primary endpoint, time to treatment failure (death or change of baseline treatment regimen) at 1 year was not different between inolimomab and ATG (unadjusted hazard ratio 0.875, 95% CI 0.56-1.38; P = 0.56)
- Severe cGVHD after 1 year was seen in 80.2% patients on inolimomab vs 75.4% patients on ATG (P >0.5)
- Subjects had worse prognosis with unrelated donor (P = 0.006) or age >60 years (P = 0.006)
- Inolimomab did not show improvement in the treatment of steroid-resistant aGVHD

Pediatrics

**Lucchini G, Labopin M, Beohou E, et al. Impact of conditioning regimen on outcomes for children with acute myeloid leukemia undergoing transplantation in first complete remission. An analysis on behalf of the Pediatric Disease Working Party of the European Group for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2017;23:467-474. https://www.ncbi.nlm.nih.gov/pubmed/27916512

- Retrospective study of European Group for Blood and Marrow Transplantation (EBMT) registry data of 631 patients 2-18 years of age undergoing MRD or MUD alloHCT for AML in CR1 from 204 centers between 2000-2010 regarding the use of 3 different conditioning regimens:

busulfan/cyclophosphamide (BuCy), TBI/cyclophosphamide (TBICy), and busulfan/cyclophosphamide/melphalan (BuCyMel).

- 109 patients received TBICy, 389 received BuCy, and 133 received BuCyMel as their conditioning regimen. The majority of patients received transplants from a MRD (73%) and bone marrow was most commonly used as the stem cell source (70%). Median patient age was 11.9 years and median follow-up time was 55 months.
- Patients receiving BuCyMel had lower incidence of relapse at 5 years (14.7% vs 31.5% with BuCy vs 30% with TBICy, $p<0.01$), higher 5-year OS (76.6% vs 64% vs 64.5%, $p=0.04$), and higher leukemia-free survival (74.5% vs 58% vs 61.9%, $p<0.005$) with comparable NRM (10.8% vs 10.5% vs 8.1%, $p=0.79$). Older age and use of peripheral blood as the stem cell source was associated with increased cGVHD and NRM and lower LFS and OS.
- Grades III-IV aGVHD rates were higher in patients receiving BuCyMel (17.6% vs 9.6% vs 6.8%, $p=0.052$) but rates of cGVHD were similar amongst the groups (35.2% vs 25.8% vs 27.8%, $p=1.00$).
- The authors concluded that among pediatric patients receiving HCT for AML in first CR, the use of BuCyMel conditioning is superior to TBICy and BuCy in reducing relapse and improving LFS.

Others

**DeFilipp Z, Duarte RF, Snowden JA, et al. Metabolic syndrome and cardiovascular disease following hematopoietic cell transplantation: screening and preventive practice recommendations from CIBMTR and EBMT. *Bone Marrow Transplant.* 2017;52:173-182.
https://www.ncbi.nlm.nih.gov/pubmed/27548466

- Collaborative review of current literature and expert opinion to provide specific screening and preventative practice recommendations of metabolic syndrome by the CIBMTR and EBMT
- About 30-50% of long-term survivors develop metabolic syndrome post-HCT with an increased risk of cardiovascular mortality by about 2-4 fold compared to the general population. Recommendations are broken down by subsections contributing to metabolic syndrome
- Abdominal obesity – consider monitoring body composition with each visit. Consider intensive, multicomponent behavioral interventions for obese patients or patients with large waist circumference. Dual-X-ray absorptiometry may be useful to monitor changes
- Dyslipidemia – lipid panel recommended at 3 months post HCT then every 3-6 months for high-risk patients. Follow existing USPSTF and NHLBI recommendations for low-risk patients.
- Hypertension – screen at every clinic visit (at least yearly). Given absence of data, follow goals from available guidelines (e.g. JNC-8). Specific goals should be tailored based on patient specifics
- Insulin resistance/diabetes mellitus – standard-risk patients: screen pediatric fasting glucose every 5 years; screen adults every 3 years if at least 45 years old or if BPs >135/80 mm Hg. High-risk patients: A1C or fasting glucose at 3 months post-HCT then every 3-6 months with goal A1C < 7%
- Coronary heart disease – no specific screening recommendations. Patients should be evaluated on a case-by-case basis of risks/benefits of electrocardiography
- Ischemic stroke – follow existing AHA/ACC and USPSTF recommendations

Abbreviations

aGVHD: acute graft versus host disease
alloHCT: allogeneic hematopoietic cell transplantation
AML: acute myelogenous leukemia
ATG: anti-thymocyte globulin
cGVHD: chronic graft versus host disease
CIBMTR: Center for International Blood and Marrow Transplant Research
CR: complete remission
GCSF: granulocyte colony-stimulating factor
GVHD: graft versus host disease
Haplo-HCT: haploidentical hematopoietic cell transplantation
HCT: hematopoietic cell transplantation
HL: Hodgkin Lymphoma
HLA: human leukocyte antigen
LFS: leukemia-free survival
MAC: myeloablative conditioning
MDS: myelodysplastic syndromes
MMF: mycophenolate mofetil
MRD: matched related donor
MUD: matched unrelated donor
NMA: non-myeloablative
NRM: non-relapse mortality
OS: overall survival
PBSC: peripheral blood stem cells
PFS: progression free survival
PR: partial remission
RIC: reduced intensity conditioning
TBI: total body irradiation
TRM: transplant-related mortality

ASBMT Pharmacy SIG Communications Working Committee:
Eric Chow, Katie Gatwood, Suzanne Gettys, Aimee Hammerstrom, Teresa Kam, Scott Lanum, Stephanie Malenfant, Ashley Newland, Ryan Shaw, Catherine Weber