This month, the GvHD Hub are focusing on prognostic factors for Graft-versus-Host Disease (GvHD). To date, the following biomarkers have shown to predict GvHD outcomes:

**Organ damage:**
- ST2: soluble receptor for IL-33, secreted by the gastrointestinal (GI) tract
- REG3α: antimicrobial peptide secreted by Paneth cells
- AREG: EGFR ligand required for tissue damage repair

**Systemic:**
- TNFR1: produced by MΦ/activated T-cells, promote gut apoptosis
- IL6 and TIM3: promote B- and T-cell recruitment/activation, inhibit T-cell apoptosis

This article summarizes some of the other prognostic factors that have been identified, contains video interviews with experts, and features highlights from upcoming presentations.

**Predictors of acute GvHD (aGvHD)**

**B7 superfamily proteins**
In February 2019, Biqi Zhou, and colleagues from The First Affiliated Hospital of Soochow University, published a retrospective study analyzing 64 patients who underwent haploidentical hematopoietic stem cell transplant (haplo-HSCT). Their aim was to investigate the prognostic impact of B7H1 and B7H3 in the development of aGvHD. A control group of 38 human leukocyte antigen (HLA)-matched patients was used. The authors analyzed the levels of B7H1, B7H3, PD1, soluble CD25, ST2 and TNFR1 levels on day zero, seven, 14 and 28 post-transplantation.

**Conclusion:** Serum levels of B7H1/B7H3 on day seven can predict grade III/IV aGvHD.

**Endothelial Activation and Stress Index (EASIX) score**
During the European Society for Blood and Marrow Transplantation (EBMT) meeting in March 2019, Miriam Sanchez-Escamilla presented results from a trial evaluating the prognostic value of the Endothelial Activation and Stress Index (EASIX) for predicting aGvHD, as well as non-relapse mortality (NRM) and overall survival (OS).

In this study, higher EASIX scores on day 30, day 100 and at the onset of aGvHD were associated with higher NRM and inferior OS, as well as predicting the incidence of high-grade aGvHD.
Predictive factors for GvHD

Conclusion: endothelial damage is a significant contributor to inferior outcomes post-allo-HSCT.

Proteome profiling

Junghoon Shin and colleagues utilized proteome profiling to analyze plasma samples from patients undergoing allo-HSCT to identify protein biomarkers to predict the risk of aGvHD. The biomarkers identified as potential predictive markers and used as biomarker panel scores (range, 0–3) were; tissue inhibitor of metalloproteinase 1, plastin-2 and regenerating islet derived protein 3-α.

Conclusion: plasma-derived protein biomarkers were able to predict aGvHD prior to the development of clinical symptoms.

Low pre-transplant serum citrulline

In 2018, Armin Rashidi and colleagues published the results of an analysis of three biomarkers (citrulline, Reg3α, and intestinal fatty acid binding protein). The levels were evaluated pre-transplant on day seven, and then post-transplant on days seven and 28 in consecutive patients undergoing allo-HSCT.

Conclusion: pre-HSCT serum citrulline level predicted patients at risk of developing aGvHD; intervening prior to HSCT to augment the gut barrier may assist in ameliorating this risk.

Villous atrophy in the terminal ileum

In a study by Yuusaku Sugihara and colleagues, ileocolonoscopy was conducted to evaluate whether it can be used to predict the severity of aGvHD following allo-HSCT. This retrospective analysis of 51 patients was conducted following symptoms of abdominal pain, anorexia, nausea, vomiting and diarrhea.

Conclusion: villous atrophy in the terminal ileum showed significant correlation with GvHD severity. The severity of villous atrophy was correlated with steroid refractoriness.

Predictors of chronic GvHD (cGvHD)

HY antibodies to predict cGvHD

Antibodies targeting Y-chromosome encoded proteins (HY antibodies), detected three months post-transplant in male HSCT recipients who received their transplant from a female donor, are significantly more likely to experience cGvHD. This multicenter, retrospective study evaluated the HY antibody levels in patients undergoing transplant to better determine this correlation. Serum samples of 234 patients were analyzed at three months and one year post-transplant for levels of the following HY antigens: DBY, UTY2, ZFY, RPS4Y, and EIF1AY.

Conclusion: The presence of HY antibodies at three months post-transplant predicts the development of cGvHD. Scoring HY levels at three months may help identify patients at high-risk for cGvHD to enable them to take part in cGvHD prevention trials.

CXCR3 ligand genes

During the 60th American Society of Hematology (ASH) meeting, Hao Dai presented data evaluating the role of the CXCR3 axis in cGvHD. Serum levels of CXCR3 ligands, including CXCL9, were evaluated pre-transplant and on day 28 post-transplant. Selected single nucleotide polymorphisms (SNPs) were then analyzed for their association with severe cGvHD.

Conclusion: the likelihood of severe cGvHD was predicted by a genetic risk group of four SNPs in the recipient’s CXCR3 ligand genes, and by serum CXCL9 levels 28 days after transplant.
Early prediction of cGvHD
Also, during this ASH meeting, the GvHD Hub spoke to Amit Kalra, University of Calgary, CA, regarding the early identification of patients at high risk of cGvHD after transplant. Watch the video below:

Amit Kalra | ASH 2018 | Early prediction of chronic GvHD

Pediatric late aGvHD versus cGvHD biomarkers

During the EBMT meeting in 2019, Kirk R Schultz presented results from the PBMT 1202 / applied biomarkers in late effects of childhood cancer treatment (ABLE) study. This study analyzed the differences between pediatric late aGvHD and cGvHD by biomarker assessment at day 100 post-allo-HSCT.

In this study, a control group of patients who did not develop cGvHD (n= 123) was compared to an experimental group who developed cGvHD (n= 44) or late aGvHD (n= 58). The investigators tested biomarker levels within 96 hours of conditioning starting on day +100, at six and 12 months post-transplant, and at the onset of cGvHD.

The results showed:

- In late aGvHD and cGvHD, transitional B-cell populations decrease, memory B-cells increase and ST2 expression levels are elevated
- In cGvHD, there were more complex abnormalities with a loss of regulatory function and an increase in additional cytokines and follicular T-helper cells.
- Conclusion: therapeutic targets may differ between late aGvHD and cGvHD.

Combination of biomarkers to predict GvHD

During the Transplantation and Cellular Therapy (TCT) Meeting held in February 2019, John E. Levine presented data evaluating the predictive accuracy of different GvHD biomarker combinations. The analysis aimed to identify the optimal combination of biomarkers at GvHD onset to predict non-relapse mortality (NRM). All potential combinations of the following were assessed: REG3a, ST2, TNFR1, and TIM3.

- Conclusion: ST2, REG3a, TNFR1, and TIM3 individually, and in combinations, were predictors of NRM. No new combinations were able to more accurately predict NRM at greater significance than already published.

Machine-learning algorithms to predict GvHD Risk

During the 2018 ASH Annual Meeting & Exposition, San Diego, US, the GvHD Hub spoke to Yasuyuki Arai, Kyoto University, Kyoto, JP, about the creation of a GvHD risk prediction model using machine-learning algorithms. Watch the video below:

Yasuyuki Arai | ASH 2018 | The role of machine-learning algorithms in GvHD risk prediction

Prognostic factors in upcoming presentations
During the upcoming ASH meeting, several abstracts surrounding prognostic factors in GvHD are due to be presented. Highlights include:

- **Donor Clonal Hematopoiesis Increases Risk of Acute Graft Versus Host Disease after Matched Related Transplantation in AML and MDS Patients**
  
  - Study summary: analysis of the effect of donor clonal hematopoiesis of indeterminate potential (CHIP) in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who received a transplant following reduced intensity conditioning, with peripheral blood stem cells (PBSCs) from older matched-related donors, and tacrolimus-based GvHD prophylaxis
  
  - Conclusion: Donor-CHIP was significantly associated with increased risk of grade II–IV and III–IV aGvHD

- **Impact of Gut Mycobiota Composition on Outcomes after Allogeneic Hematopoietic Cell Transplantation**
  
  - Study summary: analysis of the impact of fecal fungal microbiota (mycobiota) in patients undergoing allo-HSCT with an aim of identifying fungi factors associated with outcomes
  
  - Conclusion: fecal mycobiota may contribute to aGVHD as demonstrated by the higher incidence of grade II–IV aGVHD in patients colonized with higher amount of *Candida glabrata*

- **The MAGIC Algorithm Probability (MAP): A Novel Laboratory Biomarker for the Response to Treatment of Acute Graft-Versus-Host Disease**
  
  - Study summary: prospective analysis of serum samples and clinical staging of patients undergoing HSCT who received treatment for aGvHD. Serum REG3α and ST2 before and after systemic therapy for aGvHD were measured with the Mount Sinai Acute GvHD International Consortium (MAGIC) algorithm probability (MAP) calculated. The investigators hypothesized that a change in MAP between start of treatment and 28 days post-transplant could serve as a biomarker for GvHD
  
  - Conclusion: MAP is potentially the first validated laboratory test that uses biomarkers to predict response to treatment for aGVHD and is more accurately able to predict survival than clinical response after four weeks of treatment

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