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# Using microbiota to predict post-transplant mortality

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Earlier studies have suggested a connection between microbiota, post-allogeneic hematopoietic stem cell transplant (allo-HSCT) outcomes, and common complications of allo-HSCT such as relapse, graft-*versus*-host disease (GvHD), infection, and toxic organ-effects. However, most studies were performed at single centers, therefore it is unknown if these associations can be applied universally, as the potential diverse nature of the microbiota in relation to geography and institutional practice is not taken into account. For example, different transplant centers have various approaches to nutrition and antibiotics — two factors that determine microbiota injury.

To evaluate the impact of microbiota diversity on the outcomes of patients undergoing allo-HSCT at four different institutes on three continents, Jonathan U. Peled and colleagues conducted a study, recently published in the *New England Journal of Medicine*.[1]

**Study design**

- Fecal samples (8,767) were obtained prospectively from patients (N = 1,362) undergoing allo-HSCT in two cohorts at four centers
  - Cohort 1: Memorial Sloan Kettering Cancer Center, New York, US
  - Cohort 2: University Hospital Regensburg, Regensburg, DE; Hokkaido University Hospital, Sapporo, JP; Duke University Medical Center, Durham, US
- Samples were requested weekly, with a median of four samples per patient
- Samples were profiled by 16S ribosomal RNA gene sequencing
- Primary outcome: overall survival (OS)
- Other outcome parameters: transplant-related death, relapse (relapse or disease progression), and GvHD-related death
- Microbiotal diversity (alpha diversity) was calculated using the inverse Simpson index. Alpha diversity is a single value that summarizes a microbiome community by the count of unique species and how evenly their frequencies are distributed

**Patient characteristics of the total study population (cohorts 1 and 2)**

- Median patient age: 52.9 ± 0 years
- Most common indication for allo-HSCT was acute leukemia (45%)
- Most common graft type was unmodified peripheral blood stem cells (PBSCs; 43%) followed by T-cell depleted PBSCs (33%)
- Conditioning was ablative in 57% of patients, reduced intensity in 34%, and nonmyeloablative in 9%

- Mean hematologic-cell transplant comorbidity index (HCT-CI) score: 2.6 ± 0 (range, 0–11)
- Median follow-up of survivors: 25.2 months (interquartile range, 12.8–49.9)

**Periengraftment microbiota diversity and patient outcomes**

- A higher diversity of intestinal microbiota in the periengraftment period (days 7–21 posttransplant) was associated with a lower risk of death and longer survival post allo-HSCT (**Table 1**)
    - The median diversity of cohort 1 was 2.64, leading to higher diversity being defined as > 2.64 and lower diversity as ≤ 64

**Table 1.** Relationship between periengraftment microbiota diversity and survival by cohort in univariable and multivariable analysis[1]

| | **Deaths (n)** | **Univariable** | | **Multivariable*** | |
|---|---|---|---|---|---|
| **Cohort 1** | | **HR** | **95% CI** | **HR** | **95% CI** |
| Lower diversity<br><br>n = 350 | 136 | Reference | — | — | — |
| Higher diversity<br><br>n = 354 | 104 | 0.75 | 0.58–0.96 | 0.71 | 0.55–0.92 |
| **Cohort 2** | | | | | |
| Lower diversity<br><br>n = 92 | 35 | Reference | — | — | — |
| Higher diversity<br><br>n = 87 | 18 | 0.46 | 0.26–0.82 | 0.49 | 0.27–0.90 |

CI, confidence interval; HCT-CI, hematologic-cell transplant comorbidity index; HR, hazard ratio

*Multivariable adjustment for age, intensity of conditioning, graft source, and HCT-CI

**Cohort 1 | Outcome analysis and effect of graft composition and antibiotics**

- Higher intestinal diversity was associated with a lower risk of transplantation-related death but not relapse (**Table 2**)
- Effect of graft composition (unmodified T-cell replete grafts *vs* T-cell depleted grafts)
  - Microbiota diversity declined similarly
  - Patients with unmodified T-cell replete grafts:
    - Higher diversity was associated with improved survival
      - Higher *vs* lower diversity: HR 0.49; 95% CI, 0.31–0.77
    - Higher diversity was associated with a lower risk of GvHD-related death
      - Higher *vs* lower diversity: HR 0.49; 95% CI, 0.26–0.90)
  - Patients with T-cell depleted grafts:
    - No association between microbiota diversity and survival
  - Effect of antibiotics
    - Multivariable models that included exposure to piperacillin-tazobactam and meropenem (antibiotics) found an association between microbiota diversity and survival. This was associated with a decline in diversity during transplant

**Table 2**. Outcomes in cohort 1 by periengraftment microbiota diversity[1]

| | **Higher diversity (n = 354)** | **Lower diversity (n = 349)** | **HR** | **95% CI** |
|---|---|---|---|---|
| Deaths (n) | 52 | 82 | 0.63 | 0.44–0.89 |
| Relapse events (n) | 84 | 81 | 1.03 | 0.76–1.39 |

**Microbiome disruption during transplant**

- When assessing microbiota diversity
  - differences in microbiota diversity were smaller between institutes (over geography) before transplantation *versus* within one institution over time before and after transplantation
  - several lower-diversity compositions were enriched after transplantation, characterized by an abundance of *Enterococcus*, *Klebsiella*, *Escherichia*, *Staphylococcus*, and *Streptococcus*

- all four centers saw *Enterococcus* domination — a lower-diversity state associated with increased risk of vancomycin-resistant *Enterococci* bacteria and GvHD
- cumulative incidence and prevalence of domination by any taxonomic unit rose similarly across all four centers in cohorts 1 and 2

The authors concluded that microbiota disruption accompanies allo-HSCT and patterns of microbiota injury are consistent across transplant centers, but patients differ in terms of composition. There was no observed transplantation-center specific effect in relation to composition of the microbiota.

**Pre-transplant microbiota disruption and survival**

- The association between intestinal microbiota integrity and outcome was already evident in the pre-transplant period, when comparing the first samples from patients (obtained between Day −30 to Day −6) with those from healthy volunteers
- Initial samples from all four institutes had lower diversity and microbiota composition than the healthy volunteers ($p < 0.001$ for each institute)
- In cohort 1, a higher diversity in the period pre-allo-HSCT was associated with a lower risk of death and transplantation-related death (**Table 3**)

**Table 3.** Risk of death by pre-transplant diversity[1]

| | **Total cohort (n = 501)** | **HR (95% CI)** |
|---|---|---|
| Deaths (total) | 173 | |
| Higher-diversity group (n = 250) | 72 | |
| Lower-diversity group (n = 251) | 101 | 0.41 (0.24–0.71) |

**Conclusion**

The microbiota disruption exhibited during allo-HSCT was consistent across transplant centers from various geographic locations, characterized predominantly by a lack of diversity and domination by a single taxon, which was distinct from healthy control samples. A higher diversity of intestinal microbiota was associated with a lower risk of death, whereas a lower diversity was linked to higher risks of transplantation-related death and death due to GvHD.

Strengths of this study include the international design, longitudinal serial sampling, central analysis of samples, and uniform tracking of clinical outcomes. However, the population was heterogenous in relation to underlying diseases, antibiotic exposure, and graft source; the samples were not obtained at uniform time points; and only correlations can be identified, as opposed to causative relationships.

The results indicate two specific timepoints at which clinical trials may seek to remediate or prevent microbiota injury before transplantation and during the periengraftment period. Such interventions could include fecal microbiota replacement.

**References**

1. Peled JU, Gomes ALC, Devlin SM, et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2020;382:822-834. DOI: 1056/NEJMoa1900623