Title: Sugar-enriched foods exacerbate antibiotic-induced microbiome injury.

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**Abstract**

Intestinal microbiota composition is implicated in several disease states; understanding the factors that influence microbiome injury are key to understanding the interactions between host and commensal organisms and to designing microbiome-targeted therapies. We quantified how diet influences microbiome dynamics under the exposure of antibiotics. We recorded 9,419 meals consumed by 173 patients undergoing cancer treatment and profiled the microbiome in 1,009 longitudinally collected stool samples. Bayesian inference revealed associations between intake of sweets during antibiotic exposure with microbiome disruption, as assessed by diversity or expansion of the pathobiont *Enterococcus*. We validated our observations experimentally, observing that sucrose exacerbated antibiotic-induced *Enterococcus* expansion in mice. Taken together, our results suggest that avoiding sugar-enriched foods during antibiotic treatment may mitigate microbiome injury.

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**Introduction:** The intestinal microbiota modulates host immunity, and perturbations of microbiome composition are linked with various disease states (*1*, *2*). Although a precise definition of a homeostatic human microbiome composition remains elusive (*3*, *4*), a number of disease states share dysbiotic patterns in microbial community compositions, namely loss of diversity and expansion of facultative anaerobes (*5*). Understanding the factors that influence microbiome injury and dysbiosis is key to deciphering the interactions between host and commensal organisms and to designing therapeutic strategies that target the microbiome.

Host and environmental factors shape intestinal microbiome compositions; in particular, a major effect of diet has been observed both in mice and humans (*6*–*17*). Most of the human analyses, however, were conducted in volunteers in small dietary-intervention trials in subjects with chronic conditions or healthy volunteers with unperturbed, stable microbiomes (*18*). Severe perturbations, such as those which occur during acute illness or intensive medical treatment (*4*, *19*–*22*), are less well understood. Also, while animal studies suggest that dietary perturbations exert effects on microbial composition within hours (*6*, *23*–*25*) most human studies have correlated fecal microbiome compositions with long-term habitual diet (*9*, *10*, *26*–*29*) or variations on months-long timescales (*30*, *31*). Moreover, most collected dietary-intake data are based on recall-based surveys whose imprecision and limitations have been well described (*32*, *33*). Taken together, while diet is assumed to be a major determinant of microbiome composition, there exists no human data on precise diet-microbiome interactions.

Patients with blood cancers who undergo allogeneic hematopoietic cell transplantation (allo-HCT) are typically hospitalized for several weeks while they receive chemotherapy, sometimes irradiation, and antibiotics. During this time, they exhibit drastic changes in nutritional intake (*34*–*36*) as well as severe microbiome injury (*4*, *37*) characterized by a loss of a-diversity and expansion of facultative anaerobe pathobionts. These microbiome shifts are associated with adverse clinical outcomes including bloodstream infections, graft-vs-host disease, and mortality in these patients (*37*–*40*). Antibiotics (*4*, *20*, *41*, *42*) and intestinal inflammation induced by chemotherapy and irradiation (*39*, *43*) drive microbiome injury; However, whether alterations in nutrition also contribute to the dynamics of microbiome dysbiosis is thus far unclear. That these nutritional and microbiome perturbations are observed while patients are hospitalized for several weeks facilitates high-temporal-frequency collection of specimens and high-precision dietary intake recording/data collection. These precise data alongside major external perturbations akin to natural experiments can enable causal-inference approaches (*2*, *44*).

Thus, we here hypothesize that the effect of diet on microbiome composition can be quantified in the perturbed microbiome of HCT patients to reveal mechanistic insights into diet-inducible microbiome modulation. For this, we collected daily real-time dietary intake data from 173 allo-HCT recipients, paired with longitudinally collected fecal samples. We profiled fecal microbiome compositions and revealed an exacerbation by intake of sweets and simple carbohydrates (sugars) during antibiotic-induced microbiome a-diversity loss, and we validated our findings in a murine model of post-antibiotic *Enterococcus* expansion.

**Results:**

We recorded the precise intake of food items consumed during 9,419 meals (**Fig. 1A**) by 173 patients with blood cancers treated with allo-HCT between 2017-2022 (**Table 1**). Alongside, we also profiled 1,009 stool samples (median 5 samples per patient, **Fig. 1A, S1**) by 16S rRNA gene sequencing. We mapped meal records to a hierarchical food nomenclature (Food and Nutrient Database for Dietary Studies, FNDDS) that classifies foods into nested categories (*45*). A food taxonomy constructed from these categories (**Fig. 1B**) facilitated analysis of specific food types at various hierarchical aggregation levels as well as the application of metrics from ecology to summarize nutritional intake data (*11*).

HCT begins with an intensive course of chemotherapy that is intended to eliminate neoplastic cells and clear a niche for the transplanted graft. These conditioning regimens can also cause painful mouth and throat lesions (mucositis), nausea, generalized malaise, and poor appetite. Consequently, patients often have a poor diet and lose weight, during periods of increased caloric needs (*46*, *47*). These symptoms often persist until the graft is established in the bone marrow (engraftment) and produces new neutrophils—observed in this cohort after a median of 12 days (range 8-37). The severe degree of nutritional perturbation is underscored by the observation that 15 patients had such low dietary intake that they required nutrition support, either via intravenous infusion (total parenteral nutrition, TPN, n = 23 for a median of 11 days, range 2-63) or a nasogastric tube (enteral nutrition, EN, n = 5 for a median of 76 days, range 5-156). Moreover, the most frequently consumed single food item across all recorded meals were “fruit smoothies” (**Fig. 1B**), presumably due to the simplicity of their consumption and the clinical practice pattern of recommending them, along with liquid nutrition supplements (e.g., Boost®, Ensure®) in the setting of malnourishment and mucositis.

To visualize the high-dimensional dietary dataset, we applied the TaxUMAP algorithm (*4*), a modification of UMAP that takes into account the taxonomic relationships between features, in this case relationships defined by the FNDDS nomenclature (**Fig. 1C-F**). Each point represents one patient’s food consumption on a single day. We color-coded dietary records by the most abundant food group consumed (based on imputed dehydrated mass) to reveal global patterns in consumption of meals dominated by certain high-level food groupings (**Fig. 1C**). Gradients across the dietary TaxUMAP space were evident for total daily caloric intake (**Fig. 1D**), dietary a-diversity (**Fig. 1E**), and time relative to transplant day (**Fig. 1F**). This indicated that patients consumed more calories early during therapy in the form of more complex meals, an observation confirmed in plots of time *vs.* daily caloric intake (**Fig. 1G**), dietary a-diversity (**Fig. 1H**), macronutrients (**Fig. 1I**) and food-groups items (**Fig. 1J**). Despite these global dietary trends, intra-patient variability in dietary intake was highly variable (**Fig. S2**), inspiring a detailed investigation of dietary association with microbiome injury patterns.

The decline in caloric intake and dietary complexity during allo-HCT corresponded to a decline in a previously-described fecal microbiome a-diversity (*37*)(methods, **Fig. 1K**). Indeed, we observed a significant correlation between fecal bacterial a-diversity and calorie consumption as well as the magnitude of macronutrient consumption on the same day in the 158 patients with evaluable stool samples (**Fig. 1L** and **S1**). Correspondingly, we observed positive associations between caloric (and macronutrient) intake and the relative abundance of the commensal genus *Blautia* which we previously associated with longer survival after HCT and with lower mortality rates from graft-*vs*-host disease (*39*); this genus is a member of the family *Lachnospiraceae*, considered a hallmark of a healthy human microbiome (*49*). Conversely, we observed inverse associations between caloric (and macronutrient) intake and the abundance of *Enterococcus* (**Fig. 1L**), a genus that includes several pathobionts that frequently cause antibiotic-resistant bloodstream infections and is associated with adverse outcomes following HCT, including graft-*vs*-host disease and mortality (*4*, *40*, *50*, *51*).

Clinical variables that might confound these correlations include the intensity of conditioning chemotherapy regimen (**Table 1**) and antibiotic exposures. All the 173 patients received antibiotics during their diet data collection days. They were typically treated initially with prophylactic antibiotics (fluoroquinolones and intravenous vancomycin (*52*)); 138 of 173 (80%) also received broader-spectrum antibiotics during this time period, when they developed fever or other signs of potential infection (most commonly piperacillin-tazobactam, cefepime, linezolid, or a carbapenem for neutropenic fever or bloodstream infection; and metronidazole or oral vancomycin for *Clostridioides difficile* diarrhea). Such antibiotics are major drivers of dysbiosis in HCT (*4*, *20*, *41*, *42*, *53*).

To quantify the contribution of dietary intake to microbiome composition in the context of such confounding clinical variables, we developed a Bayesian model that analyzes the relationship between microbiome composition and dietary intake in the days preceding the collection of each fecal sample. We chose a dietary exposure period of two days preceding each fecal sample since variation in microbiome composition was best explained by windows of this duration in two different Procrustes analyses: one in which diet was summarized either by macronutrient composition of meals (**Fig. 2A**, dashed line), or by named food-group items (**Fig. 2A**, solid line). Notably, a two-day window was similarly found to be a good dietary predictor of microbiome composition among healthy volunteers (*11*).

The Bayesian model (**Fig. 2B**) includes treatment regimen (conditioning) intensity, nutrition-support events (TPN and EN), antibiotic exposure, and dietary intake during the prior two days as fixed-effect predictors of microbiome composition, as well as an interaction term between diet and antibiotic exposure. The model additionally includes varying-effects terms for each patient (**Fig. S4**)as well as the time relative to transplantation (that is, number of weeks hospitalized) to account for repeated observations of the same patients and capture unmeasured differences between patients, as well as unmeasured exposures other than the explicit predictors.

With this model at hand, we then first quantified the associations of antibiotics, clinical parameters, and dietary food groups with microbiome a-diversity, measured by the inverse Simpson index, taking into account patient-specific effects. We found fecal samples from recipients of the mildest conditioning regimen (“Non-ablative”) had the highest average bacterial diversity (**Fig. 2C**), consistent with our prior report (*43*). As expected, exposure to antibiotics in the prior two days was inversely associated with bacterial diversity (**Fig. 2D**) (median: -0.22, 95% Credible Interval, CI: (-0.39, -0.05)). Intake of the FNDDS food-group category “sugars, sweets, and beverages” (abbreviated here as “sweets”) while patients were exposed to antibiotics was the sole other feature clearly associated with low a-diversity (median: -0.28, 95% CI: (-0.46, -0.07)) in addition to exposure to antibiotics alone. Notably, sweets intake alone (not interacting with antibiotic exposures) was not obviously associated with changes in a-diversity (**Fig. 2D**).

We also analyzed dietary intake using macronutrient composition, which is independent of the FNDDS classification. Similarly, we identified that intake of sugars during antibiotic exposure was additive to the decline in diversity observed after antibiotic exposure (**Fig. 2E**) (median: -0.22, 95% CI: (-0.44, 0)); while intake of the macronutrient sugars alone was not associated with worse microbiome injury (**Fig. 2E**). These associations were surprising because oral nutritional supplements (e.g., Boost®, Ensure®, classified by FNDDS under the “sweets” food group, **Fig. S5**) are commonly recommended to transplant recipients (*54*, *55*). A similar result was observed in another version of the model in which we considered severity of mucositis as a potential confounder (**Fig. S6**).

Having observed a relationship between microbiome injury and co-incident exposure to antibiotics and sweets, we asked if this was apparent in the raw data, without the adjustments for the many clinical variables encoded in the Bayesian model (**Fig. 2B**). Indeed, a strong inverse relationship was apparent between grams of sweets consumed and fecal microbiota a-diversity only in samples from patients who were exposed to antibiotics (Spearman correlation 0.05, p=0.21) (**Fig. 2F**). To further explore the relationship between food groups, antibiotics, and microbiota injury in the multivariable Bayesian model, we inspected the marginal-effects plots (**Figs. 2G**). These revealed a prominent independent relationship between food intake and microbiota a-diversity only for sweets and only during periods of antibiotic exposure.

We hypothesized that sugar intake during antibiotic-induced microbiome perturbation may particularly favor expansion of bacterial taxa that we have previously reported are commonly expanded in the microbiota injury that accompanies allo-HCT (*37*). XXX (Staph, enteroococcus,…) taxa were inversely correlated with bacterial a-diversity. Of those, *Enterococcus* relative abundance was most strongly inversely correlated with a-diversity in this dataset (Spearman correlation rho: -0.32, FDR p = 1.56e-23) (**Fig. 3A** and **Fig. S7**), consistent with our prior report that *Enterococcus* expansions are the most frequent injury pattern in this population (*51*). We found that sweets consumption during antibiotic exposure correlated the relative abundance of *Enterococcus* (median: 0.67, 95% CI: (-0.01, 1.33)) (**Fig. 3B** and **Fig. S8**).

These observations in patients undergoing intensive cancer treatment suggested a model whereby antibiotic-induced microbiome injury, as manifested by loss of a-diversity and pathobiont expansion, could be exacerbated by the consumption of sweets. To test this hypothesis, we established a murine model in which microbiome disruption was induced in C57BL/6 mice with a single subcutaneous injection of the broad-spectrum carbapenem antibiotic biapenem. This reproducibly induced a moderate (2-3 log) expansion of endogenous *Enterococci* that peaked at day 3 and largely resolved by day 6 post-abx exposure, as assessed by dilution plating on *Enterococcus*-selective agar (**Fig. 3C,** upper panel). Supplementation of the standard chow diet with sucrose dissolved in a gelatin vehicle augmented the expansion of Enterococci on day 3 (median 3.53-fold, p = 0.049) and, strikingly, sustained the Enterococcal expansion median 7.30-fold by day 6 (p = 0.002). This effect of sucrose was also significant when accounting for repeated measures per mouse over time (p = 0.028, **Fig. 3C,** lower panel). Notably, sucrose treatment alone had no effect on Enterococcal burden in the absence of antibiotics. Taken together, our results provide observational evidence that consumption of dietary sugars, in the form of sweets food items, during or after antibiotic exposure decreases microbiome diversity and increases *Enterococcus* expansion, a novel microbiome-diet dynamic that we validated *in vivo*.

**Discussion:**

In this study, we analyzed a cohort of 173 heavily treated patients whose fecal microbiome profiles and dietary intake were intensively monitored longitudinally. We found that in patients with cancer undergoing hematopoietic cell transplantation intake of foods enriched in simple carbohydrates (sugars) is linked with microbiome injury, particularly when the patients were concurrently exposed to antibiotics. These microbiome injuries—either low a-diversity or relative expansion of *Enterococcus* in fecal samples—are clinically relevant as they have previously been reported to predict adverse clinical outcomes, including mortality, in several cohorts of allo-HCT recipients (*37*, *38*, *53*, *56*, *57*).

The dramatic perturbation experienced by the participants was key, as it facilitated analysis of how the microbiota responds to a profound stimulus. This “natural experiment” of longitudinal dynamics in a real-world clinically relevant setting offers opportunities for inference (*30*) that are distinct from those made in prior pioneering studies in which volunteers were profiled at presumed steady states(*10*, *11*), or assigned to specific diets (*13*, *15*, *17*, *58*–*60*). Additionally, the longitudinal design in which both fecal sampling and diet intake were collected serially may increase statistical power for causal-inference hypotheses compared with cross-sectional sampling designs (*2*).

Collection of accurate dietary-intake data in humans is challenging, owing in part to the low resolution of food-frequency questionnaires and the human fallibilities in responding to recall survey instruments (*32*, *61*, *62*). The data-collection approach utilized here is not as rigorous as weighed food records; participants circled whether they ate 0, 25%, 50%, 75% or 100% of each item. This limitation, however, was mitigated by real-time meal logging and by the fact that the vast majority of meals were prepared by a large-volume hospital cafeteria with standardized portions and recipes, the underlying data of which were used in curating the dataset. Moreover, a dietician or their assistant also met with the patients thrice weekly to review their diaries, motivate sustained participation with data collection, and clarify incomplete or inconsistent records, although this may have itself introduced bias through observer effects.(*63*)

Commonly used approaches to reduce the dimensionality of nutritional data include conventional macronutrient metrics (e.g., high fiber intake) and pre-defined diet-quality scores (e.g., Healthy Eating Index, Mediterranean Diet Score). However, associations between microbiota composition and such indices have not been consistently observed (*27*); here we looked beyond macronutrients nutrients and food-frequency habits by analyzing nearly-daily nutritional intake data considering specific food items (*11*).

Many variables in a clinically heterogeneous observational cohort can confound associations. The Bayesian analysis applied here accounted for several potentially confounding variables, including patient-level variables such as conditioning intensity and temporal sample-level exposures such as antibiotics and parenteral nutrition (*64*–*66*). The inference from patient data that sucrose and an antibiotics synergize to disrupt microbiome composition was corroborated as a causal effect in a mouse model of antibiotic-induced expansion of endogenous Enterococci that was exacerbated by sucrose supplementation. This is consistent with other reports that simple carbohydrates can induce dysbiosis and exacerbate experimental colitis or metabolic syndrome (*67*–*70*). The target of the sucrose is the subject of ongoing study; it might be utilized directly by Enterococci or might affect members of the microbiota community that ordinarily confer colonization resistance against Enterococcus (*71*). That most simple carbohydrates are absorbed in the small intestine and only a minority typically reach the colonic microbiota raises a possibility that sucrose modulates the host, which, in turn, shapes microbiota composition (*69*, *72*).

One clinical implication of these findings that evidence should be generated in clinical trials to guide nutritional recommendations during cancer treatments such as bone marrow transplantation. Outside the setting of cancer treatment, another hypothesis to evaluate is that avoiding sugar-enriched foods while taking antibiotics can mitigate microbiome disruption. Perhaps a recommendation for an abbreviated period of avoidance would be more feasible than lifelong recommendations to limit consumption of sweets for general cardiovascular health (*73*, *74*).

**Figure Legends**

**Fig. 1.** **Longitudinal microbiota data paired with high-resolution nutritional intake data.** (**A**) Histogram of 9,419 meals recorded (top) and of 1,009 evaluable stool samples collected (bottom) from 173 patients during allo-HCT, where day 0 is the day of cell infusion. (**B**) Food tree of 623 unique food items according to the Food and Nutrient Database for Dietary Studies (FNDDS) nomenclature. The tree is colored by 9 broad food groups; tree levels are derived from numeric food-code hierarchies. The length of tick marks around the outer ring indicate the average per-meal consumption of each food item. (**C**) TaxUMAP visualization of recorded meals colored by the most consumed food group on that day. (**D-F**) Same TaxUMAP visualization colored by daily caloric intake (D), daily dietary a-diversity (E), and time relative to transplantation (F). (**G**) Daily caloric intake, where each point is a patient’s daily consumption. (**H**) Daily diet a-diversity. (**I**) Daily consumption of macronutrients: carbohydrates, sugars, fibers, protein and fat. (**J**) Daily intake of the nine FNDDS food groups. (**K**) Fecal microbiome a-diversity (inverse Simpson index) of 1,009 stool samples. (G-K) lines: lines are LOWESS averages (dietary variables in red, fecal microbiome variables in blue), shading indicates 95% confidence interval. (**L**) Scatterplot visualizing correlation between dietary intake and the microbiome on the same day (944 data points, 944 daily dietary intake data with the corresponding stool samples). The columns specify nutritional metrics including daily caloric intake and daily intake of the macronutrients carbohydrates, sugars, fibers, protein and fat. Plotted by row are natural-log transformed microbiome a-diversity and the log10-transformed relative abundances of the genera Blautia and Enterococcus. The blue lines denote the linear regression line; gray shading the 95% confidence level. The rho and p are from the Spearman correlation test.

**Fig. 2.** **Consumption of sweets following antibiotic exposure predicts low fecal microbiota a-diversity**. (**A**) Procrustes scores signifies degree of correlation between average microbiome composition and dietary intake; dietary intake windows of 1, 2, 3, 4 or 5 days prior to each fecal sample were analyzed, either by macronutrient composition (dashed line) or by named food groups (solid line). (**B**) Directed acyclic graph representing the statistical model used to predict microbiome diversity or taxon abundances, which included antibiotic exposures; nutrition support modalities including total parenteral (intravenous) nutrition, (TPN), and tube feeds referred to here as enteral nutrition (EN) and dietary intake during the two days preceding the collection of each fecal sample (dashed line represents the interaction between antibiotics and food intake), as well as patient-level constants (chemotherapeutic conditioning regimen intensity), and varying-effects terms (per patient and number of weeks spent in hospital). Blue boxes indicate time-varying predictors; the gray box indicates constants. (**C**) Patient-level constants, namely the association of each conditioning intensity level with microbiome a-diversity. (**D**) Associations between fecal microbiota a-diversity and the predictors in the model; box and whiskers indicate the posterior coefficients of interactive associations between 100 grams of each food group in the two days preceding fecal sample collection, as well of the coefficients of interaction terms between each food group and antibiotic exposure. Interactions between a-diversity and exposure to TPN, EN, and antibiotics are plotted. (**E**) Posterior estimations of interactive associations between prior two-day intake of 100 grams of macronutrients and with the antibiotic exposure, as well as the exposure to TPN, EN, antibiotics' correlation with bacterial a-diversity. Protein is omitted from the model as it was highly correlated with fat; (C-E) thin lines represent 95% CIs, and thick lines 66% CIs, dots signify posterior medians, red colored lines represent the 95% CI is not crossing zero. 1009 stool samples from 158 patients. (D-E) rows on white backgrounds labeled in blue fonts are interaction terms between food and antibiotics; rows on light blue backgrounds labeled in black font are non-interactive terms. (**F**) Scatterplot visualizing the correlation between sweets consumption and ln(a-diversity) depending on whether the stool sample was exposed to antibiotics in the preceding two days. The line denotes linear regression, the shaded region the 95% confidence level. The r and p values are from Spearman correlation test. (**G**) Marginal effects plots of each food group consumption on the predicted ln(diversity) based on the different conditions: with or without antibiotics exposure in the prior two-day window while holding other variables constant. Lines represents the posterior predicted medians; shading the 95% interval. (F-G) Antibiotic-exposed samples are in red; non-exposed samples in blue.

**Fig. 3**. **Sugar and antibiotics synergize to exacerbate** **Enterococcus expansion in the gut microbiome in human and mouse.** (**A**) Spearman correlation between fecal microbiome a-diversity (inverse Simpson index) and the 5 most strongly correlated significant (FDR < 0.05) genera in either direction after. The genera exist in at least 10% of the samples with at least 0.01% relative abundance. Blue bars are genera correlated with lower diversity; yellow genera are correlated with higher diversity. Other genera are plotted in **Fig. S7**. (**B**) Associations between CLR transformed Enterococcus relative abundance and the predictors in the model; box and whiskers indicate the posterior coefficients of interactive associations between 100 grams of each food group in the two days preceding fecal sample collection, as well of the coefficients of interaction terms between each food group and antibiotic exposure. Thin lines represent 95% CIs, and thick lines 66% CIs, dots signify posterior medians, red colored lines represent the 95% CI is not crossing zero. 1009 stool samples from 158 patients. Rows on white backgrounds labeled in blue fonts are interaction terms between food and antibiotics; rows on light blue backgrounds labeled in black font are non-interactive terms. Posterior estimations of associations between temporal effects of prior two-day intake of every 100 grams of each food group on its own and with the exposure to antibiotics, as well as the exposure to TPN, EN, antibiotics' correlation with CLR transformed Enterococcus relative abundances. For the sweets\*antibiotic interaction term, 97.3% of the posterior distribution is positive. A heatmap of other genera is plotted in **Fig. S8**. (**C**) Sucrose exacerbates Enterococcus expansion following antibiotic treatment. *Upper panel*: fecal Enterococcal burden as measured by dilution plating on selective media; inset illustrates experimental setup. *Lower panel*: Data from the top panel are analyzed over time by trapezoidal area under the curve, which accounts for repeated measures from the same animals. 21-51 mice per treatment group; 2 independent experiments. The significance level was defined by Wilcoxon test. (ns: not significant, \*: P ≤ 0.05, \*\*: P ≤ 0.01, \*\*\*\*: P ≤ 0.0001)

### **Fig. S1**. Flow of patients and samples through the study.

### **Fig. S2**. Line plots illustrate the observed variation in the daily caloric intake, daily diet α-diversity, and fecal microbiota α-diversity across hospital stays. Each panel is one patient’s time course. The enlarged plot at the top left corner explains the details for every panel. The red, black, and blue line stands for the value of daily caloric intake, diet α-diversity and fecal α-diversity, respectively. The first two have values on the same numeric scale, therefore they share the same left Y axis. The microbiome α-diversity value is measured by the Y axis on the right. The X axis represents the day relative to transplant. All panels share the same Y axis on both sides as the first one, with the X axis representing different temporal ranges of available data per patient. Alphanumeric codes are patient identifiers.

**Fig. S3.** Posterior prediction check for the Bayesian model (**Fig. 2B**) with natural-log-transformed fecal microbiome α-diversity as the outcome. The observed distribution is in red; ten simulated datasets drawn from the posterior predictive distribution are plotted in teal.

### **Fig. S4**. Visualization of the baseline variation in microbiome a-diversity among patients. Each horizontal line represents a patient’s individual diversity fluctuations, as modeled in the Bayesian analysis. The thin whisker indicates the 95% CI; thick the 66% CI. The dot signifies the median value. Red dashed line highlights if the interval is crossing zero. The patients are sorted by the median posterior coefficients.

### **Fig S5**. Per-meal average consumption of the top ten foods in the “sugars, sweets, and beverages” group (referred throughout this manuscript as simply “sweets”. Dark pink bars denote the total dehydrated weight of each food’s per meal average consumption; the light pink bars represent the sugar content.

**Fig S6**. Although the Bayesian model (**Fig. 2B**) included several variables to account for health status of the participants, we reasoned that mucositis might still confound the analysis, as damage to the gastrointestinal lining can lead to translocation of luminal contents such as lipopolysaccharide (LPS), leading, in turn to fevers and to antibiotics; separately mucositis can cause pain and nausea, leading to anorexia and recommendations by clinicians to consume oral nutritional supplements (e.g. Boost, Ensure). We therefore conducted a version of the analysis in which we considered exposure to patient-controlled analgesia (PCA) opioids by intravenous pump in the two days preceding fecal-sample collection as a surrogate for severe mucositis. There were 52 (5.2%) fecal samples from 26 (15.0%) patients exposed. (**A**) Posterior coefficients of associations between 100 grams of food intake on its own in each group and with the exposure to antibiotics during the prior two-day window and bacterial a-diversity, as well as the association between exposure to TPN, EN, PCA, antibiotics and a-diversity. (**B**) Posterior distribution of the three levels of conditioning intensity with the same outcome. (A-B) thin lines represent 95% CIs, and thick lines 66% CIs, dots signify posterior medians, red colored lines represent the 95% CI is not crossing zero.

**Fig S7**. Spearman correlation between each genus relative abundance and the α-diversity of the stool sample (by Simpson reciprocal index). Genera observed in >10% of the samples at an abundance >0.01% were included. The p value from spearman correlation test is multiple hypothesis adjusted with Benjamini Hochberg method. Genera that met an FDR < 0.05 are included here. Blue bars indicate correlation with lower diversity, while yellow bars represent correlation with higher diversity.

### **Fig S8**. Heatmap visualizing association between temporal exposure to food group intakes, nutrition support as well as antibiotics and microbiome genus abundance. Genera observed in >10% of the samples at >0.01% relative abundance. Relative abundance of the genera is transformed with CLR. Red box exhibits that the 75% credible interval (CI) is positive, while blue box for 75% CI negative. Blank represents the 75% CI crosses zero. The asterisks reveal the defined significance level: one means 95% CI doesn’t cross zero, while two for 97.5% and three for 99%. Genera are ordered by hierarchical clustering with the “complete” agglomeration method with dendrogram included on the right.

# **Methods**

**Patients**

Recipients of allo-HCT at Memorial Sloan Kettering Cancer Center between 2017 and 2022 consented to IRB-supervised biospecimen collection. Neutrophil engraftment was defined as the first of three days of neutrophil count ≥500k/μl. Five patients died without achieving engraftment and were excluded from the analysis of median time to engraftment.

**Nutrition data collection and annotation**

The hospital kitchen’s commercial computer system (Computrition, Bedford, MA) was configured to provide a printout that accompanied each meal tray to the bedside upon which patients were asked to indicate, immediately after each meal, whether they consumed 0, 25%, 50%, 75% or 100% of each item they ordered for that meal. These instruments were collected by a dietician or other research team members thrice weekly, during which missing entries were completed through informal bedside interviews along with encouragement to sustain motivation with the project. Consumption data were entered into the kitchen software, which was linked to the recipe and mass of each item. Data were manually vetted by a research dietitian to correct obvious errors (e.g., grossly implausible kilocalorie values resulting from sporadic typographic errors in the hospital kitchen records).

A nine-digit food code was assigned to each unique food item according to the classification of the Food and Nutrient Database for Dietary Studies (FNDDS) (*45*). The numeric codes are structures such that subsequent numeral positions differentiate foods within larger groups. For example, “Egg omelet with whole egg” has food code 32130010, in which the first digit “3” denotes eggs, the second digit X denotes XX, and each subsequent digit conveys progressively high-resolution classifications of foods. Water fractions from the FNDDS dataset were used to compute the dehydrated weight of the consumed food. For enteral nutrition, the listed water percentage in each formulation was used to calculate non-water volumes. The dehydrated weight was computed by converting the volume to grams based on 1.05 g/mL. The analyzed dataset thus listed the grams of FNDDS food items consumed in each meal on each day of hospitalization.

### **Food tree construction**

A food tree was constructed with the 622 unique FNDDS items consumed by the patients in this cohort, as done before (*11*)(<https://github.com/knights-lab/Food_Tree>). The tree spans nine broad FNDDS food groups, namely, Grain Products (abbreviated here as “grains”), vegetables, “Meat, Poultry, Fish, and mixtrues” (abbreviated here at “meats”), “Milk and Milk Products” (abbreviated here as “milk”), “Sugars, Sweets, and Beverages” (abbreviated here as “sweets”), fruits, “Dry Beans, Peas, Other Legumes, Nuts, and Seeds” (abbreviated here as “legumes”), “Fats, Oils, and Salad Dressings” (abbreviated here as “fats”), and Eggs. In some cases, food items not explicitly classified in FNDDS contained ingredients from multiple categories (e.g., milk-based mango smoothie). We addressed this by manually categorizing foods based on which FNDDS food description they fit best to. For example, milk-based mango smoothie, despite having mango in it, fits the description of “11553110 fruit smoothie, with whole fruit and dairy”, therefore it was classified in the “Milk and Milk Products” group.

## **Dietary data analysis: taxUMAP and diet** α-**diversity**

The hierarchical organization of the FNDDS vocabulary facilitated application of a-diversities to diet data using Faith’s phylogenetic distance (*75*), which was implemented using Qiime2’s (qiime2-2021.11)(*76*) “qiime diversity alpha-phylogenetic” functionality with the faith\_pd metric. The food tree taxonomy was utilized, as well as the dehydrated weight consumption of the food item represented by food code per patient per day. The taxUMAP method (*4*) was used to visualize compositional similarities between the patients’ daily meals, similar to beta diversity. The fraction of each consumed food represented by a food code per patient per day was used to calculate the food tree taxonomy.

## **Fecal microbiome analysis**

Fecal sample inclusion criteria and flow through the study are detailed in **Fig. S1**. Microbiome profiling by 16S rRNA sequencing was performed as described (*77*). Briefly, bacterial cell walls were disrupted using silica bead-beating, nucleic acids were isolated using phenol-chloroform extraction, and the the V4-V5 variable region of the 16S rRNA gene was amplified. 16S amplicons were purified either using a Qiagen PCR Purification Kit (Qiagen, USA) or AMPure magnetic beads (Beckman Coulter, USA) and quantified using a Tapestation instrument (Agilent, USA). DNA was pooled to equal final concentrations for each sample and then sequenced on the Illumina platform. The 16S sequencing data was analyzed using the R package DADA2 (version 1.16.0) pipeline with default parameters except for maxEE=2 and truncQ=2 in filterandtrim() function(*78*), 16S Fastq files were capped at 100K reads per sample. Amplicon sequence variants (ASVs) were annotated according to NCBI 16S database using BLAST (*79*). Microbiome a-diversity was evaluated using the Simpson reciprocal index, a summary statistic of both the richness and evenness of the microbiome flora. Taxa abundances were summarized at the genus level.

## **Procrustes test**

Since we collected serial fecal samples and serial dietary intake data, a question arose as to how many prior days of dietary intake to correlate with any given fecal sample. To find the optimal time window of dietary intake to consider, we performed a Procrustes analysis, as done previously (*11*). We considered dietary data in two alternative ways, first by using the grams of consumed macronutrients per day and second by considering the specific named foods. Qiime2 (qiime2-2021.11) was used to do the Principal Coordinate Analysis (PCoA) by first converting the counts data to biom format, then to qza format, then for stool samples the Bray-Curtis distance was used for the PCoA analysis with the macronutrient data. For food-code data, the unweighted unifrac distance was used to calculate beta diversity PCoA with the food taxonomy information. The resulting principle coordinates were incorporated to compute a sum of square value using the Procrustes function from the vegan (2.5-7) package (*80*). A Procrustes score was defined as the difference between the minimal sum of squares from the five tested scenarios and the corresponding one scenario was computed.

## **Bayesian multilevel model**

### *Data preparation*

For each stool sample included, the dietary data was summarized, for macronutrient analysis, as the previous two-day average intake of sugars, fibers and fat in grams; in the food-group analysis, as the previous two-day average intake of grains, vegetables, meats, milk, sweets, fruits, legumes, fats and eggs. Gram weights were divided by 100 so that the resulting coefficients represent the expected change in the outcome variable per each 100-gram intake of the dietary component. Conditioning intensity was a three-level factorial variable comprised of (in increasing order of intensity) Nonmyeloablative (“nonablative”), reduced intensity conditioning (“reduced”), and myeloablative (“ablative”). EN and TPN were two-factor variables encoded as TRUE if the patient was exposed to EN or TPN in the two days preceding fecal collection and otherwise FALSE. Likewise, if the stool sample was collected after exposure to antibiotics in the two-day window before it, it will be true otherwise false. The antibiotics considered were piperacillin/tazobactam, carbapenems, cefepime, linezolid, oral vancomycin, and metronidazole; they were most commonly used as empiric therapy (most commonly for neutropenic fever) or in a pathogen-directed fashion (most commonly for bloodstream infections or *C. difficile* diarrhea). Prophylactic fluoroquinolones and intravenous vancomycin (*52*) were not considered. Association of foods and antibiotics with microbiome diversity were also analyzed as interaction terms, with the assumption that food correlations with microbiome will be different depending on whether the patients had antibiotics in the prior two-day window or not. Two random effects were incorporated: one for patient-level variation, which also accounted for repeated measurements from the same patient, and another for stool samples collected at different times of the patient’s hospitalization, in the format of weeks relative to transplant which was intended to capture the dramatic decline in microbiome a-diversity that occurs during transplantation. For example, the sampling window expressed in days as [-7,0) is the week before transplant, and [7,14) the second week after transplant.

When the outcome was microbiome a-diversity, it was analyzed as the natural-log-transformed Simpson’s reciprocal index. When the outcome was genus abundance, it was analyzed as centered log ratio (CLR)-transformed raw ASV count of the genus after adding a pseudo-count of 0.5 reads with the clr function in the compositions package (2.0-6) (*81*). Ninety genera with a relative abundance greater than 0.01% and exist in at least 10% of the samples were selected were selected when investigating how the model could predict taxon abundance. The genera that have.

### *Model construction and results*

brms(2.16.3)(*82*)(*83*)(*84*) and rstan(2.26.4)(*85*) packages were used to build and run the model, with a formula: log(simpson\_reciprocal) ~ 0 + ave\_fiber + ave\_fat + ave\_Sugars + ave\_fiber:abx + ave\_fat:abx + ave\_Sugars:abx + intensity + EN + TPN + abx + (1 | mrn) + (1 | timebin) for nutritional intake represented as the macronutrients, or : log(simpson\_reciprocal) ~ 0 + ave\_fruit + ave\_meat+ ave\_milk+ ave\_oils+ ave\_egg+ ave\_grain+ ave\_sweets+ ave\_legume+ ave\_veggie + ave\_fruit:abx + ave\_meat:abx + ave\_milk:abx + ave\_oils:abx + ave\_egg:abx + ave\_grain:abx + ave\_sweets:abx + ave\_legume:abx + ave\_veggie:abx+ intensity + EN + TPN + abx + (1 | mrn) + (1 | timebin) for nutritional intake represented as the food groups. The running parameter is “warmup = 1000, iter = 3000, control = list(adapt\_delta = 0.99), cores = 16, chains = 2, seed = 123”, which means the model will do 1000 warmups, and 3000 iterations in two chains, adapt\_delta is raised to 0.99 instead of 0.8 to avoid divergent transitions.

A posterior prediction check was done to investigate how the model fit (Fig. S3A). Comparing the observed data to ten draws of simulated data that is generated from the posterior predictive distribution of the model, it was shown that simulated data are similar to the observed data, hence we conclude that the model fit well.

The posterior results are plotted with ggplot (3.3.5)(*86*), tidybayes (3.0.2)(*87*) and ggpubr (0.4.0)(*88*) packages. The 66% and 95% CI are demonstrated as thicker and thinner lines on the coefficient plots, while the median is shown as a dot.

When investigating how the model could predict taxon abundance, the model formular changed to (for instance when Enterococcus was examined): CLR(Enterococcus) ~ 0 + ave\_fruit + ave\_meat+ ave\_milk+ ave\_oils+ ave\_egg+ ave\_grain+ ave\_sweets+ ave\_legume+ ave\_veggie + ave\_fruit:abx + ave\_meat:abx + ave\_milk:abx + ave\_oils:abx + ave\_egg:abx + ave\_grain:abx + ave\_sweets:abx + ave\_legume:abx + ave\_veggie:abx+ intensity + EN + TPN + abx + (1 | mrn) + (1 | timebin), with the same running parameters.

The model posterior results of the 90 genera were illustrated in a heatmap using ggplot. The blue block denotes 75% CI is negative, while the red block for the 75% CI to be positive. Blank reads as the 75% CI crosses 0. The number of stars define the different levels of significance. We defined one star reveals that 95% CI doesn’t cross 0, two stars for 97.5%, and three stars for 99%.

The marginal effects of each food group consumption on the predicted diversity are calculated with the conditional\_effects function from brms package. The method used in the function is “posterior\_epred”.

### **Patient-controlled analgesia (PCA) exposure of the patients**

Medication prescription data were first pulled for the patients. The PCA usage were identified. The prescription duration that was not relevant to this cohort was ignored. The overlap between the PCA exposure and the previous two-day window of a given microbiome sample was scrutinized. It turned out that 52 fecal samples from 26 patients had been exposed to PCA before a stool sample collection. We created a slightly different model based on the original one by adding a binary vector to determine whether the stool sample was exposed to PCA usage or not.

**Mouse experiments**

***Mouse selection***

Female C57BL/6 mice between the ages of 6-8 weeks were requested from rooms RB03 or RB04 at Jax Laboratory. We have observed that mice from these rooms present with endogenous enterococcus. The mice were single-housed and isolated for a couple of days before starting the experiment. The groups in these experiments were diet (vehicle) + antibiotic injection; diet (sucrose) + antibiotic injection; injection (vehicle) + diet (sucrose); injection (vehicle)+diet (vehicle) There were about 3-7 mice per groupc.

***Antibiotic intervention and Diet Preparation***

Each mouse was then subcutaneously injected with a one-time 2m.g dose of antibiotic. The antibiotic selected was Biapenem, after we noticed moderate blooms of enterococcus in mice treated with Biapenem. 2m.g of Biapenem was resuspended in 100ul of DPBS. For the injection (vehicle) + diet group we used 100ul of just DPBS.

Sucrose was mixed in with HydroGel® cups (ClearH2O; Cat: 70-01-502) that are 98% pure water so that 5% of the resulting 20ml was sucrose. Each experimental group that included diet (sucrose) was replenished every 48hrs. The experimental groups that included a diet (vehicle) received just 20ml of plain hydrogel replenished every 48hrs.

***Stool collection and colony counting***

Stool was collected at multiple timepoints (D0, D3 or D6) from all single-housed mice. Fresh stool was collected in a biosafety hood, directly from the mouse into a barcoded pre-weighed sterile tube. The fresh stool was kept on ice until processing. Pellets were then resuspended in 1mL of DPBS, serially diluted in DPBS and 20ul of each dilution were plated on the *Enterococcus*-selective agar. The plates were then left to culture for 48 hours in 37C standard incubator with 5% CO2. The colonies that appear in the highest dilution were counted by eye.

***Trapezoidal AUC***

The trapezoidal AUC was calculated between day 0 and day 3, as well as day 3 and day 6, respectively, for each mouse in the experimental setting, following trapezoidal rule. The day 0’s raw count was subtracted from day 3 and day 6 for each mouse before applying the trapezoidal rule. And the total trapezoidal AUC throughout the whole experimental days was the addition of the above two separate time periods’ results. The statistical test used for comparison was Wilcoxon rank sum test. (ns: not significant, \*: P ≤ 0.05, \*\*\*\*: P ≤ 0.001)

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