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Materials and Methods

Supplementary Text

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Tables S1 to S#

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

Authors: Anqi Dai1\*, Peter Adintori1, Tyler Funnell, William P Jogia, Teng Fei, Nick Waters , Melissa Docampo, Corrado Zuanelli Brambilla, Marina Burgos da Silva, Kate A. Markey, Sean M. Devlin, Annelie Clurman, Daniel Brereton, Paul Giardina, William Jogia21,22, Madhumitha Rangesa1, Sandeep Raj, Brianna Gipson, Caichen Duan21,22, Fanny Matheis21,22, Chenzhen Zhang21,22, Tatnisha Peets, Robert R. Jenq, John Slingerland, Abigail J. Johnson, Dan Knights, Antonio L.C. Gomes, Marissa Buchan, Alexis P. Sullivan21,22, Sergio A. Giralt, Miguel-Angel Perales , Marcel R.M. van den Brink1\*, Jonas Schluter21,22\*, Jonathan U. Peled1\*

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**Abstract(**The abstract should be 100-125 words**):** The gut microbiome is a promising target for therapeutic interventions due to its potential malleability. However, rational intervention targets with causal health effects are still largely unknown and we lack mechanistic insights required to control the complex gut ecosystem. Here, we quantified how diet influences microbiome dynamics under the exposure of antibiotics. We recorded 9,419 meals consumed by 173 patients and profiled the microbiome in 1,009 longitudinally collected stool samples. Bayesian causal inference revealed negative associations between sweets intake during antibiotic exposure with microbiome diversity and corresponding positive association with pathobiont *Enterococcus* abundances. We validated our observations experimentally, demonstrating that sucrose exacerbated post-antibiotic *Enterococcus faecium* expansion in mice. Taken together, our results characterize and quantify diet modulation of antibiotic-induced microbiome injury.

**Introduction:** The intestinal microbiota modulates host immunity, and perturbations of microbiome composition are linked with various disease states (Belkaid & Hand, 2014; Schluter et al., 2020). Although a precise definition of a homeostatic human microbiome composition remains elusive (Costea et al., 2018), a number of disease states share dysbiotic patterns in microbial community compositions, namely loss of diversity and expansion of facultative anaerobes (Litvak & Bäumler, 2019). 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 (Asnicar et al., 2021; David et al., 2014; Gacesa et al., 2022; Gentile & Weir, 2018; Hildebrandt et al., 2009; Johnson et al., 2019; Jumpertz von Schwartzenberg et al., 2021; Lewis et al., 2015; Tuganbaev et al., 2020; Turnbaugh et al., 2008; Wastyk et al., 2021; Wu et al., 2011). 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(Martínez et al., 2013). Severe perturbations, such as those which occur during acute illness or intensive medical treatment(Bernard-Raichon et al., 2022; Morjaria et al., 2019; Niehus et al., 2020; Schluter et al., 2023; Suez et al., 2018), are less well understood. Also, while animal studies suggest that dietary perturbations exert effects on microbial composition within hours (Desai et al., 2016; Tuganbaev et al., 2020; Turnbaugh et al., 2009; Zarrinpar et al., 2014) most human studies have correlated fecal microbiome compositions with long-term habitual diet (Asnicar et al., 2021; Bolte et al., 2021; Cotillard et al., 2022; Gacesa et al., 2022; Rothschild et al., 2018; Zhernakova et al., 2016) or variations on months-long timescales (Smits et al., 2017; Vangay et al., 2018). Moreover, most collected dietary-intake data are based on recall-based surveys whose imprecision and limitations have been well described (Archer et al., 2013; Subar et al., 2003). 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 (Baumgartner et al., 2017; Farhadfar et al., 2020; Fuji et al., 2015) as well as severe microbiome injury (Peled et al., 2020; Schluter et al., 2023) 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 (Golob et al., 2017; Jenq et al., 2015; Peled et al., 2020; Taur et al., 2012). Antibiotics(Liao et al., 2021; Morjaria et al., 2019; Schluter et al., 2023; Shono et al., 2016) and intestinal inflammation induced by chemotherapy and irradiation(Jenq et al., 2015; Shouval et al., 2022) drive microbiome injury; here, we hypothesize that alterations in nutrition also contribute to the dynamics of microbiome dysbiosis. 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 data. This precise data alongside major external perturbations akin to natural experiments can enable causal-inference approaches (Craig et al., 2017; Schluter et al., 2020).

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 sweets intake during antibiotic induced microbiome alpha 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**) consumed by 173 patients with blood cancers treated with allo-HCT between 2017-2022 (**Table 1**). We also profiled 1,009 stool samples by 16S rRNA gene sequencing (median 5 samples per patient, **Fig. 1A, S1**). We mapped meal records to a hierarchical food nomenclature (Food and Nutrient Database for Dietary Studies, FNDDS) that classifies foods into nested categories.(U.S. Department of Agriculture, Agricultural Research Service., 2018) A food taxonomy constructed from these categories (**Fig. 1B**) facilitated the analysis of food types at various hierarchical aggregation levels as well as the application of metrics from ecology to summarize nutritional intake data.(Johnson et al., 2019)

HCT begins with an intensive course of chemotherapy that is intended to eliminate neoplastic cells and clear a niche for the transplanted graft, but which can also cause painful mouth and throat lesions (mucositis), nausea, and poor appetite. Consequently, patients often have a poor diet and lose weight, despite increased caloric needs.(Andersen et al., 2020; de Defranchi et al., 2015) These symptoms often persist until the graft is established in the bone marrow 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 was “fruit smoothies” (**Fig. 1B**), presumably due to the simplicity of its 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, a modification of UMAP that takes into account the taxonomic relationships between features, which in this case were the food-group items (**Fig. 1C-F**).(Schluter et al., 2023) 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 diet were large (**­­Fig­­. S2**), inspiring a detailed investigation of its association with microbiome injury patterns.

The decline in caloric intake and dietary complexity during allo-HCT corresponded to a decline in fecal microbiome a-diversity, as seen before (Peled et al., 2020)(methods, **Fig. 1K, S2**). Indeed, we observed a significant correlation between bacterial fecal a-diversity and calorie consumption as well as the magnitude of macronutrient consumption (**Fig. 1L**), for the 158 patients with evaluable stool samples (**Fig. S1**). Correspondingly, we observed positive associations between caloric (and macronutrient) intake and the relative abundance of a commensal genus, *Blautia* which we previously associated with longer survival after HCT and with lower rates of death from graft-vs-host disease(Jenq et al., 2015); this genus is a member of family Lachnospiraceae that is a hallmark of a healthy human microbiome. Conversely, we observed inverse associations between caloric (and macronutrient) intake and the abundance of *Enterococcus*, 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.(Papanicolaou et al., 2019; Schluter et al., 2023; Stein-Thoeringer et al., 2019; Taur et al., 2012). Clinical variables that might confound these correlations include the intensity of conditioning chemotherapy regimens (**Table 1**) and antibiotic exposures. All but one of the 89 patients received antibiotics during their transplantation. They were typically treated initially with prophylactic antibiotics (fluoroquinolones and intravenous vancomycin,(Seo et al., 2014)); 70 of 89 (79%) also received broader-spectrum antibiotics, commencing at a median of transplant day 0, IQR day –3 to day +6) 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 (Holler et al., 2014; Liao et al., 2021; Morjaria et al., 2019; Schluter et al., 2023; Shono et al., 2016).

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 patient microbiome and the 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 by the macronutrient composition of meals (**Fig. 2A**, dashed line), and another in which named food-group items were considered (**Fig. 2A**, solid line). Notably, a two-day window was similarly found to be a good dietary predictor of microbiome composition among healthy volunteers.(Johnson et al., 2019)

The Bayesian model (**Fig. 2B**) includes chemotherapeutic treatment regimen 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 includes varying-effects terms for each patient as well as the time relative to transplantation to account for repeated measurements of the same patients capturing unmeasured differences between patients, as well as unmeasured exposures besides the explicit predictors.

With this model at hand, we then first quantified the associations of antibiotics, clinical parameters, and dietary macronutrients with microbiome a-diversity, measured by the inverse Simpson index, taking into account­ patient-specific effects (**Fig. S4**). We found fecal samples from recipients of the mildest conditioning regimen had the highest average diversity (**Fig. 2C**). As expected, exposure to antibiotics was inversely associated with bacterial diversity (**Fig. 2D**) (median: -0.21, 95% Credible Interval, CI: (-0.38, -0.04)). Interestingly, consumption of sugars while being exposed to antibiotics was associated with further decreases in a-diversity beyond exposure to antibiotics (median: -0.22, 95% CI: (-0.44, 0)), while sugar intake alone was not obviously associated with changes in a-diversity (**Fig. 2D**). Classifying dietary intake via FNDDS food groups, we correspondingly identified that items classified by the nomenclature as “sugars, sweets, and beverages” (here: “sweets”) also had a negative effect on microbiome a-diversity when consumed during antibiotic exposure (**Figs. 2E, S3B**) (median: -0.29, 95% CI: (-0.50, -0.09)). Again, sweets intake outside of antibiotic exposure did not have an obvious effect on microbiome diversity. These associations were alarming because nutritional supplement drinks (e.g., Boost, Ensure, classified under the “sweets” food group) (**Fig. S5**) are commonly recommended to transplant recipients [ citations]. Mucositis is frequent in our patient cohort and can confound dietary patterns; using patient-controlled analgesia (PCA) as a surrogate variable for severe mucositis, we confirmed that the dietary associations remain (**Fig. S6**).

We hypothesized that sugar intake during antibiotic-induced microbiome perturbation may particularly favor expansion of few bacteria, hence exacerbating diversity loss. We therefore ranked bacterial relative abundance correlations with diversity and found *Enterococcus* relative abundance mostly negatively associated with diversity (**Fig. 3A**) (Spearman correlation rho: -0.32, FDR: 1.56e-23) (Full results shown in **Fig. S7**). We then applied our model to investigate dietary effects on abundances of *Enterococcus* (**Fig. 3B**), as well as the most abundant bacterial genera (**Fig. S8**). In support of our hypothesis, we found that sweets consumption correlated positively with relative abundance of *Enterococcus* during antibiotic exposure (median: 0.67, 95% CI: (-0.01, 1.33)).

Our results thus suggested a model whereby antibiotic-induced microbiome injury, in the form of a-diversity loss and pathobiont expansion, could be exacerbated by the consumption of sweets. To test this hypothesis, we adopted a previously established experimental approach (CITE) to study the expansion of the pathobiont *E. faecium*: we treated mice with a cocktail of biapenem (**Fig. 3C**), which enables the bloom of *E. faecium* without a complete depletion of the commensal microbiota and provided mice with sucrose in the gel vehicle in addition to their regular chow diet. To track *Enterococcus* populations over time, we used the trapezoidal area under the colony forming unit (CFU) curve (AUC). The vehicle alone, with or without sucrose did not affect the expansion of *E. faecium* in absence of antibiotic treatment. However, when we treated mice with biapenem first, *E. faecium* CFUs per gram of fecal pellet increased significantly after antibiotic exposure (p= 7.4e-5). In support of our hypothesis—that sweets intake during antibiotic exposure exacerbated pathobiont domination—we indeed observed a significant increase in *Enterococcus* CFUs when fed the sucrose diet during antibiotic exposure (p=0.028). 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 *E. faecium* expansion, a novel microbiome-diet dynamic that we validated in vivo.

**Discussion:**

We found that in patients with cancer undergoing hematopoietic cell transplantation that that intake of foods enriched in simple carbohydrates (sugars) is linked with microbiome injury, particularly when patients were concurrently exposed to antibiotics, as measured either by low microbiome a-diversity or relative expansion of Enterococcus in fecal samples. This association, in a cohort of 173 heavily treated patients whose fecal samples and dietary intake were intensively monitored longitudinally, was observed by means of a Bayesian analysis that accounted for several confounding clinical variables. The inference from patient data that sucrose and an antibiotic synergize 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 in consistent other reports that simple carbohydrates can is induce dysbiosis and exacerbate experimental colitis (Kawano et al., 2022; Khan et al., 2020; Laffin et al., 2019; Montrose et al., 2021), but to our knowledge a synergy between antibiotics and sugars has not been previously appreciated.

A key feature of the dataset collected and analyzed here is the dramatic perturbation the subjects underwent while participating. While the statistical model took into account the differences in treatments and antibiotic exposures, broadly all the patients underwent a comparable and rather severe perturbation, that is, allo-HCT. Although potentially confounded by myriad exposures, the “natural experiment” of observing a highly dynamic period in a “real-world” patient setting can offer insights that are distinct from those made in prior pioneering studies in which volunteers were profiled at steady states [cite Asnicar/Spector and Johnson/Knights], or assigned to specific diets [cite Elinav Cell paper, Sonnenburg fiber paper, and Gary Wu hospitalization paper/vegan].

were transplanted because all participants had broadly similar perturbation, that is, allo-HCT (albeit with heterogenous details that we accounted for in the statistical model) as opposed to other perturbations such as caloric restriction that , that is bone marrow transplantation ecause we have more severe damage that 100 patients have the same type of perturbation, we are able to generalize, ‘find generic effects’ whereas Dan Knight’s pioneering prior work in healthy volunteers at steady state generalizable patterns were not able to. Difficult to discern the relationships between diet & microbiome in steady-state volunteers (this was sort of shown in Gary Wu’s experiments of veganizing people, but here we have real-world, larger cohort). Unlike previous studies

Recently a dataset generated from ?!,000? ?volunteers? microbiome were correlated with responses to food-frequency [say something about Spector/Ansciar]. The design of the present study is distinct in that there, healthy volunteers were sampled at a presumed steady state and questioned about their habitual diet, whereas we studied the response of the microbiome to a dramatic perturbation of nutrition and other insults in a clinically relevant context. In their study, Spector/Ansicar called for looking beyond macronutrients nutrients and FFQ data, here we did just that by analyzing nearly-daily data and by analyzing specific foods as opposed to macronutrients.

Collection of accurate dietary-intake data in humans is challenging [citations from google doc about how bad recall instruments are]. Our data-collection approach is not as rigorous as weighed food records as it relied on participants circling whether they ate 0, 25%, 50%, 75% or 100% of each item, however: this was mitigated by the fact that the vast majority of meals were prepared by a large-volume hospital cafeteria with standardized portions and recipes that we used in curating the dataset A dietician or trained research assistants also met with the patients thrice weekly to review their diaries, encourage sustained motivation with data collection, and clarify incomplete or inconsistent records.

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. A different clinical trial might test the hypothesis that avoiding sugar-enriched foods while taking antibiotics will mitigate microbiome disruption, even outside the setting of cancer treatment. Perhaps a recommendation for an abbreviated period of avoidance would be more feasible than recommendations to limit consumption of sweets in general for cardiovascular health. [citation]

Discussion points to make:

can compare/contrast to this paper which found that ɑ diversity was associated with “higher intakes of total vegetables, greens and beans, total fruit, and whole fruit”(Maskarinec et al., 2019)

When we talk about how we dealt with TPN and EN, can cite this mouse paper that shows that putting mice on TPN affects the microbiome.(Harris et al., 2014)

In limitations, can point out that this was still dependent largely on self-reporting that is susceptible to bias and misreporting; we attempted to address this with professional-assisted reporting, although this can also be biased because of observer effects.(Vujkovic-Cvijin et al., 2020)

Likely to omit, but copied from an earlier version of the intro: Another concern is that intake of added sugar has increased dramatically over the past few decades in the western diet,(Kopp, 2019)while numerous studies have indicated that the added sugar has detrimental effects on the microbiome well-being.(Di Luccia et al., 2015; Kawano et al., 2022; Khan et al., 2020; Montrose et al., 2021)

The amount of microbiome variation explained by the model is .... other var that could account for the variation

In the Bayesian multilevel model, we included two variables representing whether the patients had EN or TPN in the prior two days of a stool sample collection. (Harris et al. 2014) previously demonstrated that parenteral nutrition infusion alone caused changes in microbiome in mouse models.

And one limitation to how we represent the nutritional intake in food groups is that a food item with more than one component may only be classified to one food group of its major component. For example, a mango smoothie may be only categorized to the milk group in FNDDS terms since it fits the description of fruit smoothie, with whole fruit and dairy, which is a subgroup of milk and milk products, even though the smoothie also has mango in it which belongs to the fruits group. This could be biasing how we quantify the gram intake of each food group. We are exploring new ways to represent each hospital menu in greater detail, to have the nutritional intake with superior precision with more advanced database.

(Segata, 2021) identified connections between habitual diet and microbiome in 1098 healthy individuals, with the habitual diet information summarized from Food Frequency Questionnaires. They called for higher resolution nutrition intake data for future diet-microbiome studies, specifically weighted food record data. Our method of quantifying the food intake is not as rigorous as weighed food records since it relied on participants circling whether they ate 0, 25%, 50%, 75% or 100% of each item. However, this is mitigated by the fact that the vast majority of meals were prepared by a large-volume hospital cafeteria with standardized recipes and portions. We also had a research dietician or trained research assistants meet with the patients thrice weekly to review their diaries, encourage sustained motivation with data collection, and clarify incomplete or inconsistent records. Though this method was still dependent largely on self-reporting that is susceptible to bias and misreporting. We attempted to address this with professional-assisted reporting, although this can also be biased because of observer effects (Vujkovic-Cvijin et al. 2020).

(Segata, 2021) also focused on healthy individuals, while our study zoomed in on patients that were undergoing major perturbations of both nutrition and microbiome in a clinically relevant context. Our observation that dysbiosis can be exacerbated by simple carbohydrates in transplant patients is in keeping with studies that simple sugars induce dysbiosis and can exacerbate experimental colitis or metabolic syndrome (Montrose et al. 2021; Khan et al. 2020; Kawano et al. 2022; Di Luccia et al. 2015).

**Fig. 1.** **The figure caption should begin with a short descriptive statement of the entire figure followed by additional text.** Captions should be immediately after each figure. The primary callout of each figure part is indicated with a bold capital letter enclosed in parentheses [e.g., (**A**)]. Additional callouts are indicated the same way, but without the bold format. If you prefer, you can place both figures and captions logically throughout the text near where they are cited rather than at the end of the file (but not both). If a paragraph in the main text begins with the name of a figure, write out “Figure” in full (e.g., <para>“Figure 1 shows….”)

**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 food items according to the FNDDS food nomenclature. The tree is colored by 9 broad food groups, and tree levels are derived from the food-code hierarchies. The length of tickmarks around the outer ring indicate the average per-meal consumption of each food entry. (­**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 ɑ diversity (E), and transplant day (F). (**G**) Daily caloric intake. (**H**) Daily diet ɑ diversity. (I) Daily consumption of carbohydrates, sugars, fibers, protein and fat. (**J**) Daily intake of the nine food groups. (K) Microbiome ɑ diversity (inverse Simpson unit) of 1009 stool samples. (G-K) lines: LOWESS average, shaded: 95% confidence interval. Red: diet derived, Blue: stool sample derived quantities. (**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 carbohydrates, sugars, fibers, protein and fat. The rows observe microbiome ɑ diversity natural log transformed, Blautia and Enterococcus at genus level log10 transformed. The blue line denotes the linear regression line, with the gray band indicating 95% confidence level. The rho and p stand for the spearman correlation value and the p value from the test.

**Fig. 2.** **Quantification of dietary, antibacterial and nutrition support’s effects on microbiome composition**. (**A**) Procrustes scores signifying correlations between average dietary intake and microbiome when the previous 1, 2, 3, 4 or 5 days are considered (dashed line: macronutrient data, solid line: food group consumption data). (**B**) Diagram of the directed acyclic graph representing the statistical model; antibiotic exposure, nutrition support (TPN and EN) and dietary intake during the past two days relative to a stool sample (dashed line representing the interaction between antibiotics and food intake), as well as patient-level constants (chemotherapeutic conditioning intensity), and varying effects terms (per patient and for weeks spent in hospital) are used to predict microbiome diversity or taxon abundances. Blue boxes indicate time varying predictors, the gray box indicates constants. (**C**) Patient level constants, namely the effects of different intensity level’s association to microbiome ɑ-diversity. (D) Posterior estimations of associations between temporal effects of prior two day intake of every 100 grams of sugars, fiber and fat on its own and with the exposure to antibiotics, as well as the exposure to TPN, EN, antibiotics' correlation with bacterial ɑ-diversity (in blue background indicating its temporal nature); (E) 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 ɑ-diversity, as well as the association between exposure to TPN, EN, antibiotics and ɑ-diversity. (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 (n=1009 stool samples from 158 patients).

**Fig. 3**. Enterococcus bloom following antibiotic exposure in both human and mouse data. (A) Spearman correlation between ɑ diversity of the stool sample in Simpson reciprocal unit and top 5 significant (FDR < 0.05) genera that had the largest correlation in either direction after Benjamini Hochberg adjustment. The genera exist in at least 10% of the samples with at least 0.01% relative abundance. Blue bars indicate correlation with lower diversity, while yellow bars represent correlation with higher diversity. (B) 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. Thin lines represent 95% CIs, and thick lines 66% CIs, dots signify posterior medians, salmon-colored lines represent although slightly crossing zero line, the sweets intake under antibiotic exposure is mostly positive with 97.3% of the posterior distribution being positive. (C) Mouse experiments testing sucrose’s causal effect on Enterococcus colony blooming. The diagram illustrates experimental setups, signaling antibiotics or vehicle administering time and the timepoints of stool sample collection after diet vehicle or sucrose treatment. Enterococcus raw colony counts on day 0- day 3 and day 6- timepoints in mice groups of different antibiotics or diet treatment are shown. The mice underwent either biapenem antibiotics treatment or injection vehicle. They were fed with either sucrose or diet vehicle in diet treatment. The significance level was defined by Wilcoxon test. (ns: not significant, \*: P ≤ 0.05, \*\*\*\*: P ≤ 0.001)

### Fig. S1. Diagram that documents the selection criteria of the stool samples and also the resulted number of patients in this cohort.

### Fig. S2. Line plot that illustrates the observed variation in the daily caloric intake, daily diet ɑ diversity, and fecal ɑ diversity across patients’ hospital stays. Each panel reads one patient’s time course in this cohort. The zoomed 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 ɑ diversity and fecal ɑ diversity, respectively. The first two have values at the same numeric scale, therefore they share the same Y axis denoted on the left. The microbiome ɑ diversity’s value is measured by the Y axis on the right. The X axis represents the day relative to transplant of each data point. All the other panels share the same Y axis on both sides as the first one, with the X axis representing different ranges of day relative to transplant for each patient.

Fig. S3**.** Accompanying figure for the Bayesian model with natural log transformed microbiome ɑ diversity as the outcome. (A) observed natural log transformed microbiome ɑ diversity distribution as well as ten simulated datasets drawn from the posterior predictive distribution. (B) Posterior distribution of the three levels of conditioning intensity with the same outcome.

### Fig. S4. Visualization of the baseline difference in microbiome ɑ diversity among patients. Each horizontal line represents a patient’s individual diversity fluctuations. The thin line stands for 95% CI, and the thick line stands for 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 in ascending order.

### Fig S5. Per-meal average consumption of the top ten foods in the sugars, sweets, and beverages group. Dark pink bars denote the total dehydrated weight of this food’s per meal average consumption, while the light pink bars represent the sugar subpart.

Fig S6. The results for the multilevel Bayesian model with additional binary predictor indicating whether the patient was exposed to patient-controlled analgesia (PCA) as a surrogate for severe mucositis in the prior two days of a stool sample collection. 52 fecal samples from 26 patients had exposure. (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 ɑ-diversity, as well as the association between exposure to TPN, EN, PCA, antibiotics and ɑ-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 qualifying genera’s relative abundance and the ɑ diversity of the stool sample in Simpson reciprocal unit. The genus is selected if it exists in at least 10% of the samples with at least 0.01% relative abundance. The p value from spearman correlation test is multiple hypothesis adjusted with Benjamini Hochberg method. The genus that satisfies 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. The genus is selected if it exists in at least 10% of the samples with at least 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 selection**

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 a the first of three days of neutrophil count above or equal to 500k/ul. Five patients died without achieving engraftment and were excluded from the analysis of median time to engraftment.

**Nutrition data collection and annotation**

Data were exported from the Computrition foodservice software systems (<https://www.computrition.com/>) with the name of the recipes, as well as the served and eaten portions of the food. The associated kilocalories, carbohydrates, protein, fat, sugar, fiber, and sodium in gram weight were also included. Exported data were then vetted by the research dietitian and cleaned by the computational biologist to correct discrepancies in nutrient data (i.e., grossly inaccurate kilocalorie values) and impute missing nutrient data.

A nine-digit food code was assigned to each of the unique food items according to the classification of the Food and Nutrient Database for Dietary Studies (FNDDS), developed by the United States Department of Agriculture (USDA). For instance, the food “Egg omelet with whole egg” is annotated with the food code 32130010. The unique codes are developed to differentiate foods within larger food groups (i.e., all foods in the eggs category begin with the number 3). Finally, we used the food code to obtain the water portion of a food item per 100 kilocalories of each food, which is used to compute the dehydrated weight of the consumed food.

Similarly, the water percentage in each of the enteral nutrition formulas was identified, and the non-water volumes were calculated. The dehydrated weight was computed by converting the volume to grams based on 1.05 g/mL.

Our data resolves the grams of USDA food items consumed in each meal on each day of their 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 (<https://github.com/knights-lab/Food_Tree>). The tree spans nine broad food groups, namely, grains, vegetables, meats, milk, sugars & beverages, fruits, legumes, fats and eggs.

## **Dietary data analysis: taxUMAP and diet ɑ diversity**

The hierarchical organization of the FNDDS vocabulary facilitated application of ɑ diversities to diet data using Faith’s phylogenetic distance(Faith, 1992). It was implemented using Qiime2’s (qiime2-2021.11)(Bolyen et al., 2019, p. 2) “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 was used to unveil compositional similarities between the patients’ daily meals, similar to beta diversity(Schluter et al., 2023). The fraction of each consumed food represented by a food code per patient per day was used to do the calculation as well as the food tree taxonomy.

## **Stool sample selection and microbiome data processing**

The workflow of stool sample selecton is detailed in Fig. S1. For the 16S rRNA sequencing, bacterial cell walls were disrupted using silica bead-beating, nucleic acids were isolated using phenol-chloroform extraction, and the V4-V5 variable region of the 16S rRNA gene was amplified with polymerase chain reaction (PCR). 16S amplicons were purified either using a Qiagen PCR Purification Kit (Qiagen, USA) or AMPure magnetic beads (Beckman Coulter, USA) and quantified using a Tape station instrument (Agilent, USA). DNA was pooled to equal final concentrations for each sample and then sequenced using the Illumina MiSeq platform as previously described in previous publications(Peled et al., 2020). 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(Callahan et al., 2016), 16S Fastq files were capped at 100K reads per sample. Amplicon sequence variants (ASVs) were annotated according to NCBI 16S database using BLAST(Altschul et al., 1990). Microbiome ɑ diversity was evaluated using the Simpson’s 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**

How much of the past dietary intake data ought to be considered? To find the optimal time window of dietary intake to consider, we performed a Procrustes analysis, as done previously(Johnson et al., 2019). We considered dietary data in two alternative ways, first by using the grams of consumed macronutrients per day and second by considering the exact food items consumed represented by the Food code. We averaged the dietary intake for one- and up to five days prior to the date of a stool sample.

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 macronutrients 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(Oksanen et al., 2022). And a Procrustes score that was defined as the difference between the minimal sum of squares from the five scenarios and the corresponding one scenario was computed. This analysis confirmed that the nutrition intake in the prior two-day window has the best correlation with the following stool sample microbiome profile.

## **Bayesian multilevel model construction**

### *Data preparation*

For every stool sample we included, the dietary data was summarized as the previous two-day average intake of sugars, fibers and fat in grams, in the macronutrient system, or the average intake of grains, vegetables, meats, milk, sweets, fruits, legumes, fats and eggs, in the food group system. And the gram weight is divided by 100, so that the resulting coefficients represent change in the outcome per 100-gram intake of the dietary component. Conditioning intensity are three level factorial variables that include non-ablative, reduced, ablative levels. EN and TPN are two factor variables that if the patient had EN or TPN in the previous two days before a stool sample collection, it will be true otherwise false. Likewise, if the stool sample was collected after exposure to empirical antibiotics in the two-day window before it, it will be true otherwise false. The empirical antibiotics include piperacillin/tazobactam, carbapenems, cefepime, linezolid for neutropenic fever and oral vancomycin, metronidazole for *C. difficile* infection. Prophylactic fluoroquinolones and intravenous vancomycin were not considered. The association of food and antibiotics with microbiome diversity was shown as interactive terms, with the assumption that foods’ correlation 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 to account for repeated measurements from the same patient, another for stool samples collected at different times of the patient’s hospitalization, in the format of weeks relative to transplant. For example, [-7,0) means the week before transplant, and [7,14) the second week after transplant.

When the outcome is microbiome ɑ diversity, it’s shown as the natural log transformed Simpson’s reciprocal index. When the outcome is genus abundance, it’s denoted as centered log-ratio (CLR) transformed raw ASV count of the genus while adding a pseudo count of 0.5. The clr function in the compositions package (2.0-6) was used for the transformation(Boogaart et al., 2023). 90 genera were selected when investigating how the model could predict taxon abundance. The genera that have a relative abundance greater than 0.01% and exist in at least 10% of the samples were selected.

### *Model construction and results*

brms(2.16.3)(Bürkner, 2018)(Bürkner, 2017)(Bürkner, 2021) and rstan(2.26.4)(Stan Development Team, 2022) 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 is similar to the observed data, hence we conclude that the model fit well.

The posterior results are plotted with ggplot (3.3.5)(Wickham, 2016), tidybayes (3.0.2)(Kay, 2022) and ggpubr (0.4.0)(Kassambara, 2020) 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%.

### **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 group.

***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.

The sucrose was mixed in with HydroGel® cups (ClearH2O; Cat: 70-01-502) that are 98% pure water so that 5% of the resulted 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 different 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-weight sterile tube. The fresh stool is kept on ice and resuspended in 1mL of DPBS. The stock solution is serially diluted in DPBS. 20ul of each dilution is plated on the enterococcus selective agar. The plates are then left to culture for 48 hours in 37C standard incubator. The colonies that appear in the highest dilution are 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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