Randomized Double-Blind Phase II Trial of Fecal Microbiota Transplantation Versus Placebo in Allogeneic Hematopoietic Cell Transplantation and AML

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ABSTRACT

PURPOSE Gut microbiota injury in allogeneic hematopoietic cell transplantation (HCT) recipients and patients with AML has been associated with adverse clinical outcomes. Previous studies in these patients have shown improvements in various microbiome indices after fecal microbiota transplantation (FMT). However, whether microbiome improvements translate into improved clinical outcomes remains unclear. We examined this question in a randomized, double-blind, placebo-controlled phase II trial.

METHODS Two independent cohorts of allogeneic HCT recipients and patients with AML receiving induction chemotherapy were randomly assigned in a 2:1 ratio to receive standardized oral encapsulated FMT versus placebo upon neutrophil recovery. After each course of antibacterial antibiotics, patients received a study treatment. Up to three treatments were administered within 3 months. The primary end point was 4-month all-cause infection rate. Patients were followed for 9 months.

RESULTS In the HCT cohort (74 patients), 4-month infection density was 0.74 and 0.91 events per 100 patient-days in FMT and placebo arms, respectively (infection rate ratio, 0.83; 95% CI, 0.48 to 1.42; $P = .49$). In the AML cohort (26 patients), 4-month infection density was 0.93 in the FMT arm and 1.25 in the placebo arm, with an infection rate ratio of 0.74 (95% CI, 0.32 to 1.71; $P = .48$). Unique donor bacterial sequences comprised 25%-30% of the fecal microbiota after FMT. FMT improved postantibiotic recovery of microbiota diversity, restored several depleted obligate anaerobic commensals, and reduced the abundance of expanded genera Enterococcus, Streptococcus, Veillonella, and Dialister.

CONCLUSION In allogeneic HCT recipients and patients with AML, third-party FMT was safe and ameliorated intestinal dysbiosis, but did not decrease infections. Novel findings from this trial will inform future development of FMT trials.

ACCOMPANYING CONTENT

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INTRODUCTION

Patients with AML and recipients of allogeneic hematopoietic cell transplantation (HCT) experience major disruptions to their intestinal microbiota.[1,2] Dysbiosis patterns in these patients are largely similar[3] and characterized by microbiota community domination,[4-6] diversity loss,[7-9] and pathogen outgrowth.[10-12] Dysbiosis has been associated with mortality,[7,8] acute graft-versus-host disease (aGVHD),[13-20] poor immune reconstitution,[21-23] and relapse.[24,25] Fecal microbiota transplantation (FMT) has been successful in ameliorating dysbiosis[26-32] and treating refractory aGVHD.[33-38] However, whether FMT-mediated modulation of the microbiota prevents subsequent adverse clinical outcomes remains unclear. Most reported FMT trials in these patients have been small, single-arm, and open-label trials, with a microbiota endpoint as the primary objective.

To evaluate the clinical efficacy of FMT when used as a prophylactic approach, we conducted a randomized, double-blind, placebo-controlled phase II trial using a third-party, oral encapsulated product and with a clinical primary end point. We chose infection as the primary end point because (1) it has a high clinical burden, (2) commensal microbiota

CONTEXT

Key Objective

Does fecal microbiota transplantation (FMT) decrease infection rates in allogeneic hematopoietic cell transplantation recipients and patients with AML?

Knowledge Generated

In a randomized double-blind placebo-controlled trial, third-party oral FMT was safe but did not decrease infections. FMT ameliorated intestinal dysbiosis by restoring microbiota diversity and commensal bacteria and reducing the abundance of pathobionts.

Relevance *(C.F. Craddock)*

The feasibility and safety of prospective interventional trials of FMT in patients with hematological malignancies undergoing intensive chemotherapy or allo-SCT is demonstrated. Larger randomized trials with clinically relevant endpoints are now indicated in this important patient population.*

*Relevance section written by *JCO* Associate Editor Charles F. Craddock, MD.

enhance antiinfective immunity not only against intestinal pathogens but also distant infections of extraintestinal origin,[39] and (3) various types of infection after HCT and induction chemotherapy (eg, bloodstream,[5,6,40,41] Clostridioides difficile [CDI],[42] and respiratory tract infections[43-45]) have been associated with intestinal dysbiosis.

METHODS

Trial Oversight

This trial (ClinicalTrials.gov identifier: NCT03678493) was conducted in two parallel independent cohorts of adults treated at the University of Minnesota: allogeneic HCT recipients (HCT cohort) and patients with AML receiving inpatient induction chemotherapy (AML cohort). The Protocol (online only) was approved by our institutional review board and opened to accrual in September 2019. All patients provided written informed consent. Safety monitoring and stopping rules are detailed in the Data Supplement (Supplementary Methods 1, online only).

The trial reached its accrual goal for the HCT cohort in February 2022 after 72 HCT recipients received dose 1. Because of slow accrual in the AML cohort, this cohort was closed to new accrual at the same time. Patients who had already been enrolled but had not yet received dose 1 (two patients) continued on study and were included in the analysis. Data cutoff and unblinding occurred on August 5, 2022, once the last subject in each cohort completed follow-up for the last clinical end point.

Study Design

Patients age 18 years and older were enrolled in this randomized, double-blind, placebo-controlled, phase II trial at the time of admission to the hospital to start conditioning for a T-replete allogeneic HCT or induction chemotherapy for AML. A second set of eligibility criteria were checked when absolute neutrophil count (ANC) reached >1 $\times$ 10^9/L from nadir and antibacterial antibiotics (except those used for Pneumocystis jirovecii prophylaxis) were discontinued for 2 days. If all acute toxicities had resolved to grade 2 or lower at that time and patients were able to swallow capsules and had no evidence of relapse/progression, they received the first study treatment (dose 1). This occurred within 3 days of confirming eligibility, usually on the same day. Consented patients who did not reach the time point for second eligibility screening and those who reached that time point but did not meet the criteria for dose 1 were replaced.

Simple randomization was used to assign patients in a 2:1 ratio to receive third-party FMT or placebo in the form of five oral capsules taken all at once. Details of treatment administration are provided in the Data Supplement (Supplementary Appendix). For patients re-exposed to antibacterial antibiotics after dose 1, up to two more doses of the same type (one dose per exposure) were given until 3 months after consent. The criteria for redosing were similar to those used for dose 1. The protocol did not recommend any changes to the standard of care. We generally use acyclovir for viral, an azole for fungal, and levofloxacin for bacterial prophylaxis for the duration of neutropenia (ANC <1 $\times$ 10^9/L), and cefepime for empiric frontline treatment of neutropenic fever. Patients were followed for 9 months.

The primary end point was all-cause infection rate within 4 months after dose 1. Both microbiologically and clinically documented infections were included. Microbiological documentation included a positive culture or clinically consistent findings from other microbiological assays (eg, polymerase chain reaction). Controversial cases were resolved after consultation with the infectious diseases team. Blood culture isolates considered to be skin-associated

bacteria (including viridans group *Streptococcus* spp. and coagulase-negative *Staphylococcus* spp.) were classified as bloodstream infection (BSI) if the organism was recovered in ≥2 blood culture sets.[46] Clinically documented infection was defined by compelling clinical evidence without a positive microbiological workup (eg, fever and a new lung infiltrate). Secondary end points included specific types of infection (bacterial, viral, or fungal), grade II-IV aGVHD[47] (HCT cohort only), and BSI within 7 days after each dose.

Study product manufacturing is detailed in the Data Supplement (Supplementary Appendix). Each FMT capsule contained ≥1 × 10^{11} bacteria with ≥40% viability and each dose consisted of five capsules. This dose was previously found to be effective in treatment of recurrent CDI.[48] Product from four different donors was used and each patient received material manufactured from a single donor.

Statistical Analysis

The two cohorts were analyzed independently. The only study procedure that occurred between the two eligibility screening time points was the collection of baseline samples after consent, and only objective criteria (neutrophil recovery and discontinuation of antibacterial antibiotics) were used to determine the second eligibility time point. All patients who met both eligibility criteria were included in safety and efficacy analyses. The expected all-cause infection density in the control arms of both cohorts was 0.9-1.3 events per 100 patient-days in the first 4 months after day 30 of chemotherapy or transplantation, on the basis of our institutional pilot and published data.[49] Using Poisson rates to model recurrent event data in each arm, their ratio as measure of treatment efficacy, and a variance-stabilized test statistic, we calculated that a minimum of 72 patients in each cohort would provide 80% power to detect a 50% lower rate of infection in the FMT arm compared with the placebo arm at a two-sided alpha level of 5% (PASS 14, NCSS, LLC, Kaysville, UT). An expected rate of 1.3 events per 100 patient-days was considered for the placebo arm in both cohorts. The intervention was a package defined as up to three treatments within 4 months after dose 1. The objective of the study was to evaluate whether the experimental package as a whole would reduce infections starting with dose 1. With this definition and considering that infection rate over 4 months rather than time to the first infection was the measured end point, we did not censor patients at the time of second or third dose.

Infection data were summarized using infection density. Mean cumulative number of events, estimated by the Nelson-Aalen method,[50] was plotted for each arm. The recurrent infection data were compared between the two arms of each cohort using the multiplicative intensity method developed by Wang et al,[51] which models the occurrence of recurrent events by a subject-specific nonstationary Poisson process via a latent variable. The treatment arm was considered as the predictor and death as an informative terminal event. This method shares the same spirit as the joint frailty scale-change model but treats death events as informative censoring rather than terminal events.[52] *Post hoc* multivariable regression was performed in the HCT cohort to adjust for conditioning intensity because of its large, by-chance imbalance between the two arms. Package *reReg* in R 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for both preplanned and *post hoc* analyses of the primary end point,[52] with 95% CIs and *P* values estimated from 1,000 bootstraps. A two-sided $P < .05$ was considered statistically significant. The cumulative incidence of grade II-IV aGVHD until 6 months after HCT was calculated in the HCT cohort with death as a competing risk and compared between the two arms using a Gray's test. Post hoc Fine and Gray multivariable proportional-hazard modeling was used to adjust for the GVHD prophylactic regimen, which was not balanced between the two arms. The sample collection schedule and methods for microbiota sequencing and analysis are detailed in the Data Supplement (Supplementary Methods 2).

RESULTS

All patients meeting both sets of eligibility criteria were treated. The HCT cohort included 74 patients (FMT, 49; placebo, 25) who received 1 (58 patients), 2 (13 patients), or 3 (3 patients) study treatments. The AML cohort included 26 patients (FMT, 18; placebo, 8) who received 1 (16 patients) or 2 (10 patients) study treatments. There was no loss to follow-up and no missing data (Fig 1).

HCT Cohort

Baseline characteristics were balanced between the two arms (Table 1), except more patients (63.3% *v* 36.0%) in the FMT arm received reduced-intensity conditioning and fewer (44.9% *v* 76.0%) received GVHD prophylaxis using a post-transplantation cyclophosphamide (PTCy) backbone. Thirty-three of the 34 patients receiving myeloablative conditioning also received PTCy, indicating multicollinearity between GVHD prophylaxis and conditioning intensity. Given the randomized group assignment, we considered the imbalance in one of these variables to have occurred by chance and the imbalance in the other variable followed due to multicollinearity. All patients were exposed to antibacterial antibiotics before dose 1 (Data Supplement [Supplementary Fig 1]), which was given at a median of 23 (range, 12-62) and 26 (range, 11-63) days after HCT in FMT and placebo arms, respectively. Six patients in the FMT arm and three in the placebo arm died during follow-up. Deaths in the FMT arm were due to aGVHD (three patients), idiopathic pneumonia syndrome (one patient), cryptogenic organizing pneumonia (one patient), and seizure (one patient). All three deaths in the placebo arm were due to relapse.

Grade 3+ adverse events (AEs) are summarized in the Data Supplement (Supplementary Table 1). The most frequent of such events in the FMT arm was aGVHD, occurring as a Common Terminology Criteria for Adverse Events grade 3+ AE in 9 (18.4%) patients versus none in the placebo arm. BSI

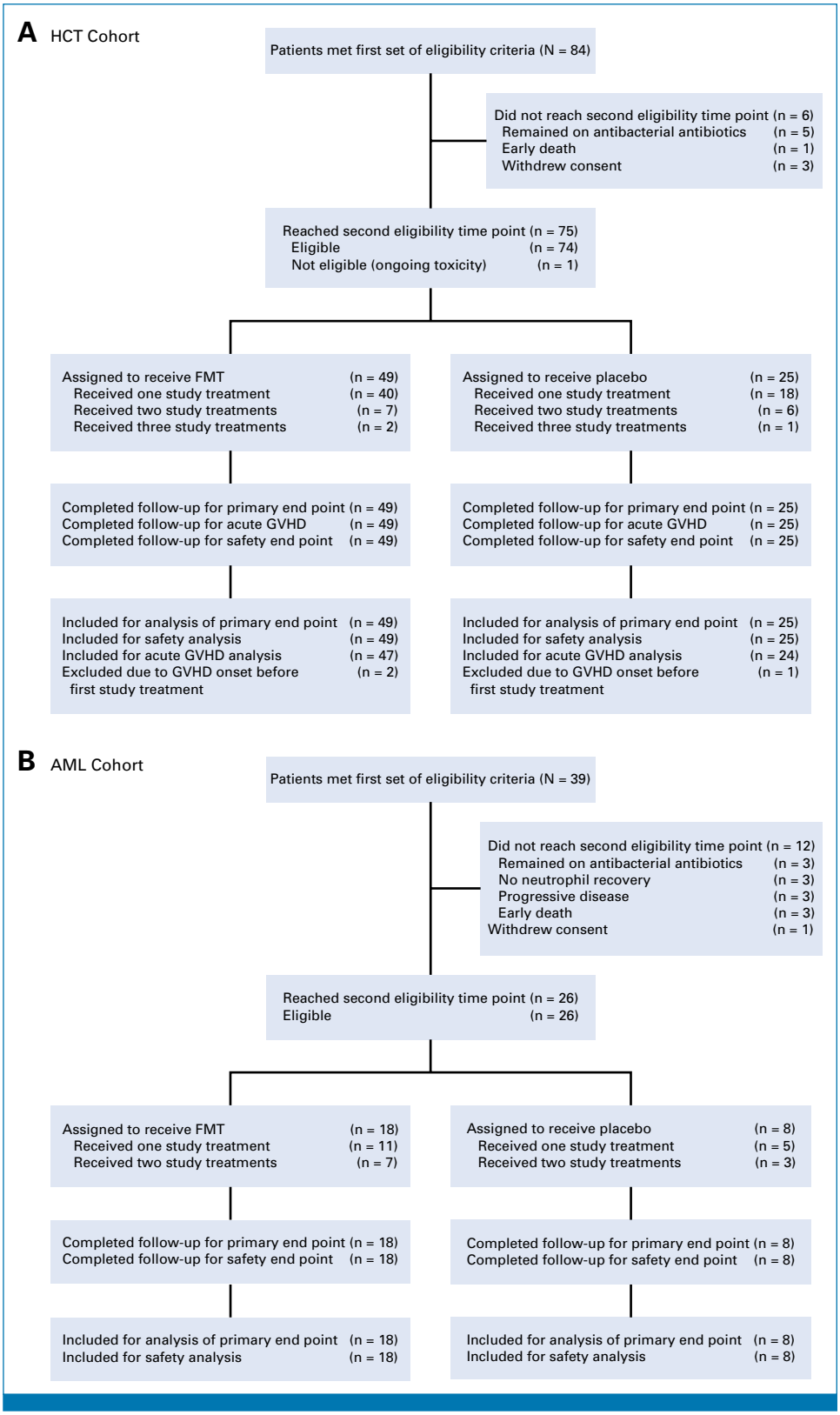

FIG 1. CONSORT diagram: (A) HCT cohort and (B) AML cohort. FMT, fecal microbiota transplantation; GVFD, graft-versus-host disease; HCT, hematopoietic cell transplantation.

occurred in 8 (16.3%) FMT recipients versus 3 (12.0%) placebo patients. Details of BSIs are provided in the Data Supplement (Supplementary Table 2). No grade 3+ AE occurred within 24 hours of a dose. There was only 1 grade 3+ GI AE (diarrhea) within 7 days after FMT. BSI within 7 days after FMT occurred in one patient. This was a case of cytomegalovirus (CMV)

TABLE 1. Baseline Characteristics

HCT Cohort			
Variable	FMT (n = 49)	Placebo (n = 25)	Total (N = 74)
Age at transplant, years			
Mean ± SD	54.2 ± 14.6	48.8 ± 15.6	52.4 ± 15.0
Male sex, No. (%)	26 (53.1)	16 (64.0)	42 (56.8)
Underlying disease, No. (%)			
Acute leukemia	33 (67.3)	20 (80.0)	53 (71.6)
MDS/MPN	7 (14.3)	2 (8.0)	9 (12.2)
Nonmalignant disorders	6 (12.2)	2 (8.0)	8 (10.8)
CLL/NHL	3 (6.1)	1 (4.0)	4 (5.4)
HCT-CI, No. (%)			
Median (range)	2 (0-8)	2 (0-5)	2 (0-8)
0-1	22 (44.9)	8 (32.0)	30 (40.5)
2 or greater	27 (55.1)	17 (68.0)	44 (59.5)
HCT donor, No. (%)			
Matched unrelated	32 (65.3)	17 (68.0)	49 (66.2)
Matched sibling	14 (28.6)	6 (24.0)	20 (27.0)
Haploidentical	2 (4.1)	2 (8.0)	4 (5.4)
Cord blood	1 (2.0)	0 (0)	1 (1.4)
Conditioning intensity, No. (%)			
Reduced intensity	31 (63.3)	9 (36.0)	40 (54.1)
Flu/Cy/low-dose TBI	25	8	33
Cy/ATG	2	0	2
Other	4	1	5
Myeloablative	18 (36.7)	16 (64.0)	34 (45.9)
Cy/TBI	17	16	33
Flu/Bu4	1	0	1
HCT graft source, No. (%)			
Peripheral blood	40 (81.6)	21 (84.0)	61 (82.4)
Bone marrow	8 (16.3)	4 (16.0)	12 (16.2)
Cord blood	1 (2.0)	0 (0)	1 (1.4)
GVHD prophylaxis, No. (%)			
Tac/MMF/PTCy	22 (44.9)	19 (76.0)	41 (55.4)
MMF/Tac	25 (51.0)	6 (24.0)	31 (41.9)
Other	2 (4.1)	0 (0)	2 (2.7)
ATG, No. (%)			
Not used	36 (73.5)	21 (84.0)	57 (77.0)
Used	13 (26.5)	4 (16.0)	17 (23.0)
Dose 1, days from HCT			
Median (range)	23 (12-62)	26 (11-63)	24 (11-63)
Doses administered, No. (%)			
1	40 (81.6)	18 (72.0)	58 (78.4)
2	7 (14.3)	6 (24.0)	13 (17.6)
3	2 (4.1)	1 (4.0)	3 (4.1)

AML Cohort			
Variable	FMT (n = 18)	Placebo (n = 8)	Total (N = 26)
Age at start of chemotherapy, years			
Mean ± SD	54.0 ± 12.1	54.9 ± 9.99	54.3 ± 11.3
Male sex, No. (%)	8 (44.4)	5 (62.5)	13 (50.0)

(continued on following page)

TABLE 1. Baseline Characteristics (continued)

AML Cohort			
Variable	FMT (n = 18)	Placebo (n = 8)	Total (N = 26)
Disease, No. (%)			
De novo	11 (61.1)	6 (75.0)	17 (65.4)
Secondary/treatment-related	7 (38.9)	2 (25.0)	9 (34.6)
Induction type, No. (%)			
7 + 3 or similar	15 (83)	8 (100)	23 (88)
ATRA + ATO	3 (17)	0	3 (12)
Inductions, No. (%)			
1	14 (77.8)	6 (75.0)	20 (76.9)
2	4 (22.2)	2 (25.0)	6 (23.1)
Dose 1, days from start of chemotherapy			
Median (range)	43 (25-78)	38 (27-67)	42 (25-78)
Doses administered, No. (%)			
1	11 (61.1)	5 (62.5)	16 (61.5)
2	7 (38.9)	3 (37.5)	10 (38.5)

Abbreviations: 7 + 3, cytarabine plus an anthracycline (with or without additional agents; Vyxeos was included in the same class); ATG, antithymocyte globulin; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; Bu, busulfan; CI, comorbidity index; CLL, chronic lymphocytic leukemia; Cy, cyclophosphamide; Flu, fludarabine; FMT, fecal microbiota transplantation; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; PTCy, post-transplantation cyclophosphamide; Tac, tacrolimus; TBI, total-body irradiation.

viremia and the only event that counted toward the stopping rule. The patient was CMV-seropositive and their HCT and FMT donors were both CMV-seronegative, making a relationship with FMT unlikely.

Seventy infections occurred during the infection monitoring window (Data Supplement [Supplementary Figs 2A and 2B], Data Supplement [Supplementary Table 3]). The infection density within 120 days after dose 1 was 0.74 and 0.91 events per 100 patient-days in FMT and placebo arms, respectively. At 120 days after dose 1, the mean cumulative number of events per patient was 0.89 (95% CI, 0.60 to 1.19) and 1.09 (95% CI, 0.55 to 1.64) in the FMT and control arms, respectively, with an infection rate ratio of 0.83 (95% CI, 0.48 to 1.42; P = .49; Fig 2A). After adjusting for conditioning intensity, the infection rate ratio declined to 0.70 (95% CI, 0.38 to 1.30; P = .26; Data Supplement [Supplementary Table 4]). Subgroup analysis for bacterial and viral infections did not indicate a treatment effect (Data Supplement [Supplementary Table 5]). The number of events was not large enough for FMT donor-specific subset analysis.

Sixteen grade II-IV aGVHD events (14 with GI involvement) occurred by day 180 after HCT, with a cumulative incidence of 29.8% (95% CI, 16.5 to 43.0) and 8.3% (95% CI, 0 to 19.6) in FMT and placebo arms, respectively (P = .05; Fig 2C). The cumulative incidence of grade II-IV aGVHD with GI involvement was 25.8% (95% CI, 13.1 to 38.6) and 4.3% (95% CI, 0 to 12.9) in FMT and placebo arms, respectively (P = .03; Fig 2D). After adjustment for GVHD prophylaxis, the hazard ratio for FMT versus placebo was 3.1 (95% CI, 0.6 to 14.2; P = .15) for grade II-IV aGVHD and 5.5 (95% CI, 0.7 to 44.0; P = .11) for grade II-IV aGVHD with GI involvement (Data Supplement [Supplementary Table 6]). Further adjustment for conditioning intensity was not possible due to multicollinearity. All 6 cases of stage III-IV GI aGVHD and all three fatal cases of aGVHD occurred in the FMT arm.

AML Cohort

Baseline characteristics were balanced between the two arms (Table 1). All patients were exposed to antibacterial antibiotics before dose 1 (Data Supplement [Supplementary Fig 1]), which was given at a median of 43 (range, 25-78) and 38 (range, 27-67) days after starting chemotherapy in FMT and placebo arms, respectively. One patient (FMT arm) died during follow-up, due to relapse. Grade 3+ AEs are summarized in the Data Supplement (Supplementary Table 1). The most frequent of such events in the FMT arm was BSI, occurring in 10 (55.6%) patients versus 2 (25.0%) patients in the placebo arm. Details of BSIs are provided in the Data Supplement (Supplementary Table 2). No grade 3+ AE occurred within 24 hours and no grade 3+ GI AE within 7 days after FMT. No event counted toward the stopping rule.

Thirty-two infections occurred during the infection monitoring window (Data Supplement [Supplementary Figs 2C and 2D], Data Supplement [Supplementary Table 3]). The infection density within 120 days after dose 1 was 0.93 and 1.25 events per 100 patient-days in the FMT and placebo arm, respectively. At 120 days after dose 1, the mean cumulative number of events per patient was 1.12 (95% CI, 0.57 to 1.67) and 1.50 (95% CI, 0.35 to 2.65) in FMT and control arms, respectively, with an infection rate ratio of 0.74 (95% CI, 0.32

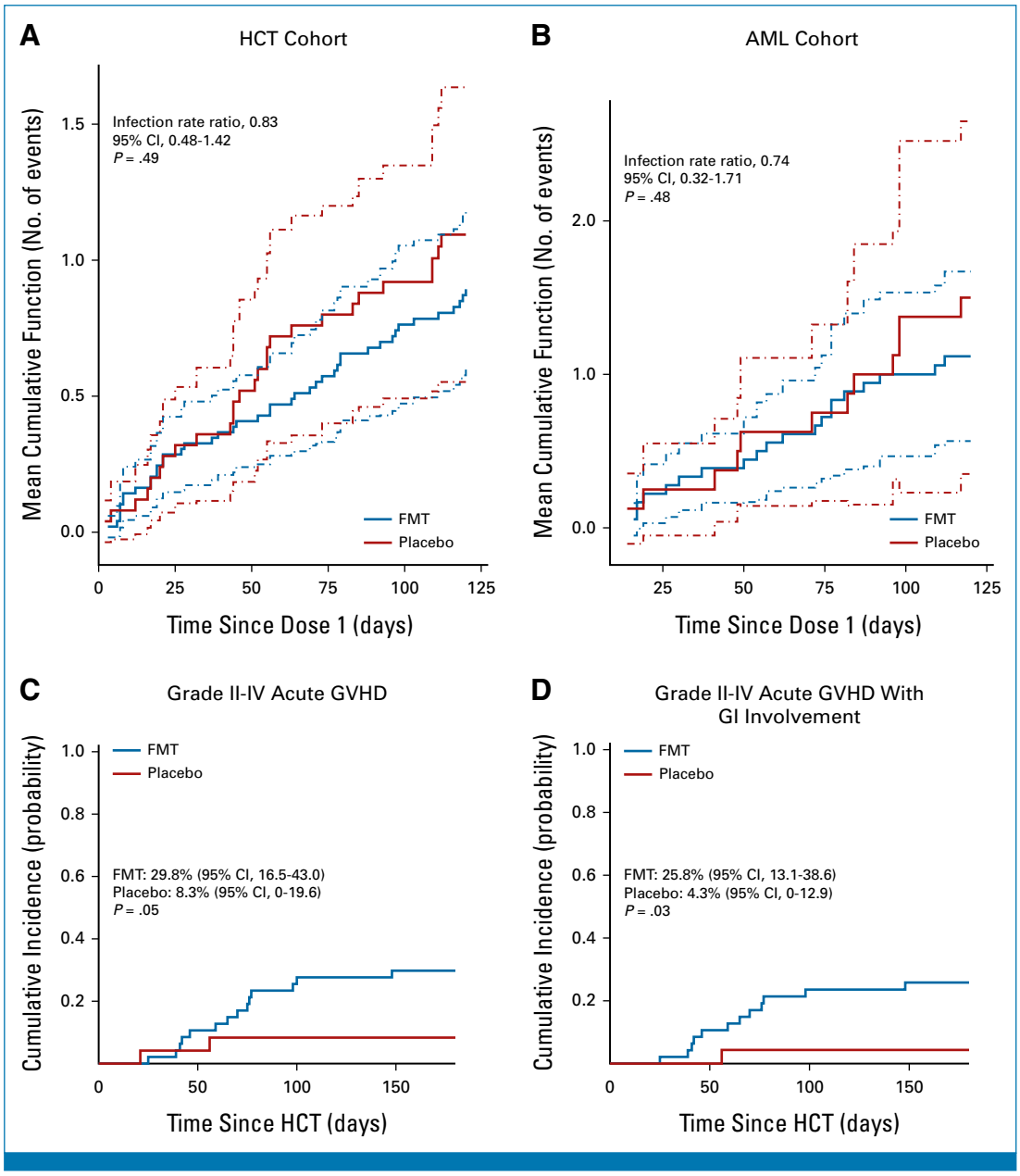

FIG 2. Analysis of the primary and secondary end points. The mean cumulative number of infection events in each arm: (A) HCT cohort and (B) AML cohort. Infection rate ratios are unadjusted and compare FMT to placebo. 95% CIs are shown as dashed lines. Cumulative incidence of (C) grade II-IV acute GVHD overall and (D) grade II-IV acute GVHD with GI involvement in the HCT cohort. FMT, fecal microbiota transplantation; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation.

to 1.71; $P = .48$; Fig 2B). Subgroup analysis for bacterial and viral infections did not indicate a treatment effect (Data Supplement [Supplementary Table 5]). Six patients in the FMT arm and five in the placebo arm proceeded to HCT. Of these, four patients and one patient developed grade II-IV aGVHD, respectively.

Microbiota Effects of FMT

After preprocessing and filtering, 287 stool samples containing 2,126 unique amplicon sequence variants ASVs (5 phyla, 27 families, and 45 genera) were analyzed. Microbiota in HCT and AML cohorts clustered together (Data Supplement [Supplementary Fig 3A]), consistent with similar patterns of injury and recovery as reported previously.[3] Thus, we combined these cohorts in future analyses. No clustering per treatment arm was apparent at baseline ($P = .27$; Fig 3A) or before dose 1 ($P = .85$; Fig 3B).

Even at baseline, patient microbiota clustered away from donor microbiota, indicating injured communities (Data Supplement [Supplementary Fig 3B]). Patient microbiota at

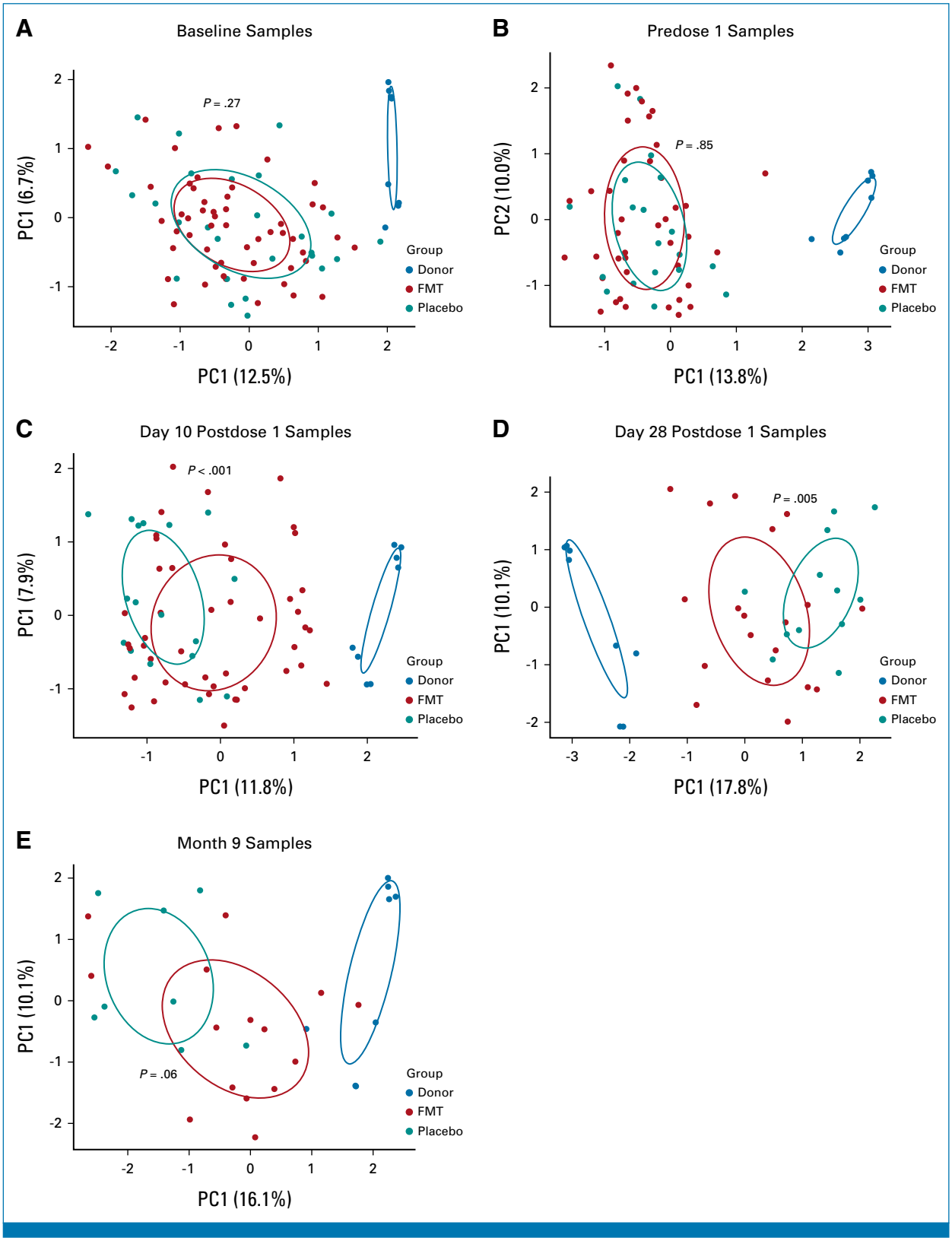

FIG 3. Microbiota clustering per treatment arm at each time point. (A) Baseline, (B) predose 1, (C) day 10 postdose 1, (D) day 28 postdose 1, and (E) month 9. Principal component analysis using Aitchison distances, with numbers in parentheses indicating the proportion of variation explained by the corresponding axis. Each point is a fecal sample and samples with similar microbiome composition are closer together in the plot. 95% confidence ellipses for group centroids are shown. *P* values are from an adonis test with 999 permutations and compare samples in FMT versus placebo arms. FMT, fecal microbiota transplantation; PC, principal component.

baseline was enriched in frequently pathogenic (eg, Enterococcus, Staphylococcus), mucolytic (Ruminococcus gnavus/torques groups),[53] and typically oral (eg, Rothia,[54] Dialister[55]) genera and depleted in several obligate anaerobic bacteria (eg, Faecalibacterium) known to produce butyrate.[56] Expansion of mucolytic bacteria in patients with acute leukemia and HCT recipients has been reported.[18,40,57-59] Further expansion of genera such as Enterococcus and Staphylococcus and depletion of the largely butyrogenic family Lachnospiraceae and genera Blautia, Roseburia, and Faecalibacterium occurred between baseline and before dose 1 (Data Supplement [Supplementary Fig 4]).

Postintervention samples clustered according to the treatment arm (Figs 3C-3E), with post-FMT microbiota moving toward donor microbiota, indicating an FMT effect. Post-FMT samples were enriched in obligate anaerobic commensal families Coriobacteriaceae (eg, genus Collinsella) and Rikenellaceae (eg, genus Alistipes), whereas postplacebo samples were enriched in Streptococcus, Enterococcus, Veillonella, and Dialister (Data Supplement [Supplementary Fig 5]). FMT was highly effective in decreasing Enterococcus and Dialister, which had expanded greatly before dose 1 and restoring Collinsella, which had drastically declined before dose 1 and failed to have any spontaneous recovery after placebo. Both

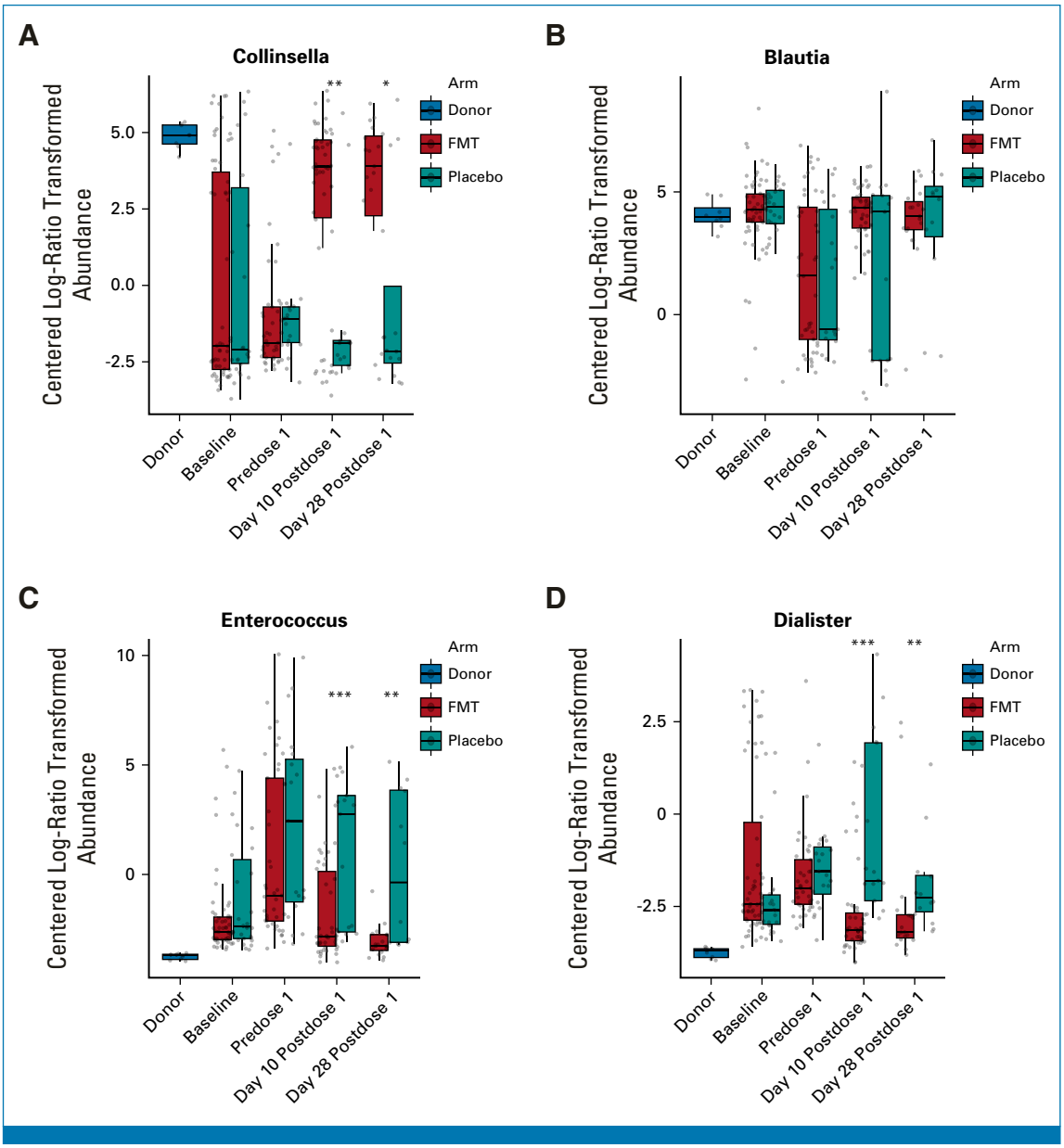

FIG 4. Effect of FMT on the abundance of select genera: (A) Collinsella, (B) Blautia, (C) Enterococcus, and (D) Dialister. Centered log-ratio abundances are shown. The horizontal line within each box shows the median. *P < .05, **P < .01, ***P < .001. P values are from a Wilcoxon test and compare the two arms at each time point. FMT, fecal microbiota transplantation.

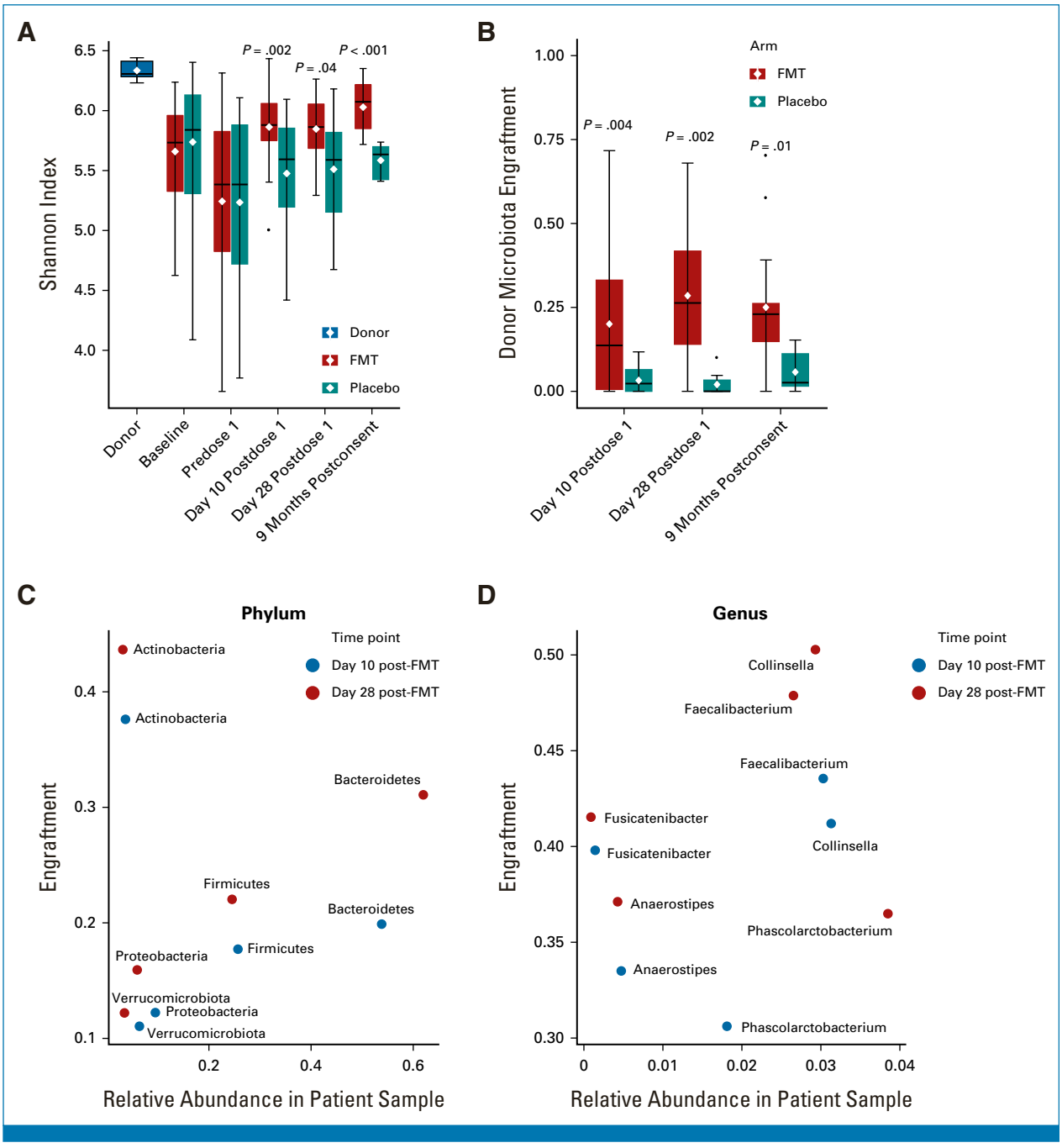

FIG 5. Alpha diversity and donor microbiota engraftment. (A) Alpha diversity, as measured by Shannon's index. (B) Donor microbiota engraftment in day-10 postdose, day-28 postdose, and 9-month postconsent samples as determined by SourceTracker. SourceTracker estimates the attribution of microbiota in a post-treatment sample to donor microbiota. In choosing the donor source for each post-FMT sample, only the specific donor whose product was administered to the patient was used as donor. By contrast, because placebo capsules did not contain any donor material, the calculated engraftment rates from all four presumptive donors were averaged to derive donor attribution of postplacebo microbiota. There were 77 post-FMT and 37 postplacebo samples in this analysis. The distribution of samples across time points was 60 samples at 10 days post-treatment, 31 samples at 28 days post-treatment, and 23 samples at 9 months. As expected, donor attribution of postplacebo microbiota was minimal. The horizontal line within each box indicates the median and the white diamond indicates the mean. *P* values comparing FMT and placebo arms are from a Wilcoxon test. The relationship between (C) phylum- and (D) genus-level engraftment rates and relative abundances at days 10 and 28 post-FMT. The *x*-axis shows the mean relative abundance of the taxon of interest in post-FMT samples, and the *y*-axis shows the attribution of that taxon to donor microbiota. FMT, fecal microbiota transplantation.

arms showed Blautia recovery toward donor levels (Fig 4). Microbiota alpha diversity was similar at baseline and predose 1 between the two arms. After treatment, while diversity in postplacebo samples showed slight recovery over time, it did not reach baseline values. By contrast, diversity in post-FMT samples significantly increased and even exceeded baseline (Fig 5A).

Sustained donor microbiota engraftment of approximately 25% was achieved (Fig 5B; Data Supplement [Supplementary Analysis 1]). Taxa with the largest donor attribution were Actinobacteria (genus Collinsella), Faecalibacterium, Fusicatenibacter, and Anaerostipes (Figs 5C and 5D). Faecalibacterium and Anaerostipes are butyrate producers[60] depleted in aGVHD.[61] Exploratory analyses did not offer a microbiome explanation for the higher incidence of aGVHD in the FMT arm (Data Supplement [Supplementary Analysis 2]).

DISCUSSION

To our knowledge, we conducted the first randomized, double-blind, placebo-controlled trial of third-party FMT with a clinical primary end point in allogeneic HCT recipients and patients with AML. Because some degree of spontaneous microbiota recovery is expected to occur after normalization of diet and discontinuation of antibiotics, randomization uniquely positioned us to evaluate the additional effects of FMT on the trajectory of microbiota recovery. Several novel observations were made. First, FMT was highly effective in decreasing the fecal abundance of Enterococcus and oral bacteria such as Dialister. Enterococcus expansion has been associated with aGVHD,[62] BSI,[5,6] and mortality.[4] Similarly, ectopic colonization of oral bacteria in the gut has been associated with colitis and inflammatory bowel disease.[63] Second, FMT was essential for the recovery of Collinsella. Collinsella depletion has been associated with neutropenic fever after HCT[64] and microscopic colitis.[65] This genus elicits systemic immunoglobulin responses in inflammatory bowel disease[66] and has been associated with response to FMT in patients with ulcerative colitis.[67] At least one strain of Collinsella is known to produce butyrate.[68] Finally, Blautia showed equivalent recovery in both arms, arguing against an essential FMT impact. Blautia depletion has been associated with an increased risk of fatal aGVHD.[69] FMT improved microbiota diversity, consistent with a previous randomized trial.[30]

Although these favorable effects on the microbiota support the potential efficacy of FMT in preventing adverse clinical outcomes associated with microbiota injury such as aGVHD, infections, and mortality, we could not demonstrate improved outcomes in the FMT arm. We chose all-cause infections, rather than a specific infection type/site, as the primary end point to test whether FMT could modulate systemic immunity not only against infections of intestinal origin but also distant-site infections originating from extraintestinal pathogens. As an example, the gut microbiota has been linked to susceptibility to respiratory tract infections.[43-45] Including infections unrelated to the gut microbiota in the same composite end point might have diluted a potential protective FMT effect. For safety reasons, we did not administer the study product before hematopoietic engraftment. With the pre-engraftment period being the highest-risk interval for infections,[70] the incidence of a large fraction of infections could not be influenced by FMT, and this might have also diluted an overall beneficial effect. FMT did not result in BSI, similar to a recent report.[71] Strict donor and product evaluation was key in this safety and should continue in future studies.

The unexpected higher incidence of aGVHD in the FMT arm is best explained by the imbalance in the GVHD prophylactic regimen between the two arms despite randomization. Grade II-IV aGVHD rates in the control arm where GVHD prophylaxis was predominantly PTCy-based were markedly lower than our historical rates without PTCy (8.3% *v* approximately 40%). The high frequency of PTCy use in the placebo arm likely decreased aGVHD incidence. In addition, the trial was not powered for aGVHD as a secondary end point and the number of events was small.

The optimal schedule and route of administration of FMT is unknown. Most studies have administered FMT on a single day or on two consecutive days. FMT was administered as oral capsules over 2 days at a median of 27 days after HCT in a previous trial, with improvement in microbiota indices.[29] Besides oral encapsulated form,[29,35,38] FMT has been administered by enema,[26,28,30] via nasogastric/nasoduodenal tube,[26,27,31,33,36] or by upper[32] or lower endoscopy.[34] The source of FMT has been third-party[26,27,31,32,34,36] or autologous,[28,30] with no compelling comparative data. We preferred a third-party product because many patients have already been exposed to antibiotics by the time their own stool could be banked for FMT. Patient subsets more likely to benefit from FMT are also unknown. In one study, 25 allogeneic HCT recipients were randomly assigned after neutrophil engraftment to receive autologous FMT versus no intervention.[30] A unique aspect of this study was that only patients with a low fecal abundance of Bacteroidetes were treated. The most frequent time frame for FMT in HCT recipients has been after neutrophil engraftment, consistent with the observed association between microbiota diversity at the time of engraftment and transplant-related mortality.[7] Some studies administered FMT before HCT to eradicate pre-existing MDROs.[32]

The minimum required engraftment for clinical efficacy is also unknown.[33,35] Our engraftment rate is in the same range as in previous FMT trials in patients with AML and HCT patients.[29,34,36] The current product (single dose, same dose range) yielded engraftment rates of 50%-60% in patients with CDI.[72] The reasons for a lower engraftment rate in this trial are unclear but likely include more severe mucoepithelial damage and a less-receptive environment for new microbiota. With short-amplicon sequencing, donor

engraftment results may underestimate true engraftment rates. This is because while novel donor strains often replace related strains of the same species in the patient, completely novel donor species are less likely to be competitive against the patient's indigenous microbiota.[73] Because taxonomy deeper than the genus level is not reliable in short-amplicon sequencing, unique donor strains (and even species) cannot be identified with certainty. Shotgun sequencing can partially overcome this barrier.

In conclusion, this randomized, double-blind placebo-controlled trial confirmed safety of FMT and its efficacy on the microbiota in patients with AML and patients with allogeneic HCT. The findings from this trial should inform the design of future definitive trials. A randomized trial in allogeneic HCT recipients with acute GVHD as the primary end point and with stratification for GVHD prophylaxis and conditioning intensity is warranted. Our observed small effect size for infection argues against using infection as the primary end point in future trials unless several hundred patients can be enrolled. If such a large trial is infeasible, we recommend limiting the inclusion criteria to patients with known or likely more severe microbiota injury (eg, recent CDI or pathogen colonization, exposure to antianaerobic antibiotics) in whom the impact of FMT may be greater. In the AML cohort, we enrolled only patients receiving inpatient chemotherapy. The increasing use of novel primarily outpatient antileukemia regimens reduced the pool of eligible inpatients, thereby slowing accrual. FMT trials targeting such patients who also have significant antibiotic exposure and likely develop dysbiosis will be of interest. Finally, a larger total microbiota dose delivered over several days might improve engraftment and potentially treatment efficacy.

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DISCLAIMER

The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Double-Blind Phase II Trial of Fecal Microbiota Transplantation Versus Placebo in Allogeneic Hematopoietic Cell Transplantation and AML

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