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Concise Communication

Lactobacillus bloodstream infections genetically related to probiotic use in pediatric hematopoietic cell transplant patients

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Abstract

We describe a cluster of 6 pediatric hematopoietic cell transplant recipients with *Lactobacillus* bacteremia attributed to probiotic use. *Lactobacillus* isolates cultured from probiotics and patients' blood were proven to be related using whole-genome sequencing. Clinical studies are needed to evaluate the safety of probiotic use in immunocompromised patients.

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Lactobacillus-containing probiotics are increasingly used as a dietary supplement in patients with gut disorders to promote gut flora.[1] However, the safety of probiotics in immunocompromised patients has not been established. In November 2019, a cluster of *Lactobacillus* bacteremia was investigated at a pediatric oncology and hematopoietic cell transplant (HCT) center. Here, we report the findings of the cluster investigation and its relation to probiotics use.

Methods

Potential sources were identified by chart review and staff interview. Patients with *Lactobacillus* bacteremia from January 2017 to December 2019 were identified using microbiology records. This study was approved by the institutional review board.

In July 2018, the Pharmacy and Therapeutics Committee approved a high-potency probiotic use in HCT patients with gut graft-vs-host disease (GVHD), multidrug-resistant organism (MDRO) colonization, or *Clostridioides difficile* infection. This probiotic (product 1) was used until March 2019 and contained 112.5 billion colony-forming units (CFU) per capsule of a proprietary blend of *Streptococcus thermophilus*, *Bifidobacterium breve*, *B. lactis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, and *L. helveticus*. In March 2019, due to shortage, product 1 was replaced by product 2 which contains the same composition. In October–November 2019, both products were available for patient use. Percent probiotic utilization in hospitalized HCT patients was calculated as the number of probiotic days divided by the number of patient days ×100. Probiotic days was defined as the total number of hospitalized HCT patients receiving probiotics per day over the month.

The remaining patient supply and unopened bottles of products 1 and 2 were cultured at an environmental laboratory (Aerobiology Laboratory Associates, Washington, DC). Probiotic lot numbers were not recorded in the patients' records. However, only 1 lot each of product 1 and 2 were used during the cluster period. *Lactobacillus* was selectively isolated from the probiotic products and was sequenced along with *Lactobacillus* blood isolates at the hospital molecular laboratory. Relatedness between the clinical and probiotic *Lactobacillus* isolates was evaluated using core-genome multilocus sequence-typing pipelines Ridom SeqSphere+ (Ridom Bioinformatics, Münster, Germany). The *L. paracasei* pipeline included 1,604 core targets, 1,010 accessory targets, reference strain ATCC334 (NC_008526.1), and 26 query genomes. The *L. plantarum* pipeline included 1,262 core targets, 1,713 accessory targets, reference strain WCFS1 (NC_004567.2), and 98 query genomes. Minimum spanning trees for each pipeline were created using 2,614 (*L. paracasei*) and 2,975 (*L. plantarum*) columns for distance calculation. Isolates with <20 allele difference were considered related.

Results

Overall, 6 patients with *Lactobacillus* bacteremia from August to November 2019 were identified as hospitalized HCT patients receiving *Lactobacillus*-containing probiotics. During the cluster period, 34 hospitalized HCT patients received at least 1 day of probiotics, of whom 6 (17.6%) developed *Lactobacillus* bacteremia. For baseline, only 1 patient (rate, 0.22 per 1,000 patient days) developed *Lactobacillus* bacteremia in 2017, 4 patients (1.04 per 1,000 patient days) developed *Lactobacillus* bacteremia in 2018, and none in January–July 2019. This incidence increased to 6 patients (4.7 per 1,000 patient days) who developed *Lactobacillus* bacteremia in August–November 2019 (Supplementary Fig. S1).

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Table 1. Description of Hematopoietic Cell Transplant Recipients with *Lactobacillus* Bloodstream Infections due to Probiotics

Patient	Age/Sex	Primary diagnosis	Transplant type, days post-transplant	Engrafted	Hospital day at positive blood culture	Presentation at bacteremia onset	Isolate from blood culture	Time to positivity of blood culture (hours)	No. of Days with positive cultures	MBI-LCBI	MDRO Colonization	Gut GVHD	Diarrhea	Neutropenia	Mucositis	NG or G-tube	Sepsis	ICU transfer	CVC removal	Antibiotic, duration	Probiotic Product, dose, and duration before bacteremia	Outcome
1	10m/M	SCID	Autologous +103	Yes	3	CVC contamination with stool	*Lactobacillus sp. (one lumen only)*	89.50	1	No	CRE/ESBL	No	Yes	No	No	No	No	No	Yes	Ampicillin and cefepime, 7 days	Product 2. 2 caps BID 20 days	Recovered
2	11m/F	ALL	Allogeneic +79	Yes	21	Fever	*L. plantarum*	10.45	6	Yes	ESBL	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Meropenem, 5 days; piperacillin/ tazobactam, 10 days	Product 2. 2 caps BID 19 days	Recovered
3	4y/M	NB	Autologous +6	No	15	Fever	*L. rhamnosus*	33.49	7	Yes	ESBL	No	No	Yes	Yes	Yes	No	NA	No	Penicillin, 10 days	Product 2. 2 caps BID 6 days	Recovered
4	16y/M	AML	Allogeneic +9	No	19	Fever	*L. casei/paracasei/ zeae (one lumen only)*	77.26	1	Yes	ESBL	No	Yes	Yes	Yes	No	No	No	No	Vancomycin, 3 days	Unknown. 2 caps QD 17 days	Recovered
5	15y/M	AML	Allogeneic +12	Yes	28	Fever	*Lactobacillus sp.*	31.26	2	Yes	No	No	Yes	No	Yes	Yes	No	No	No	Penicillin, 10 days	Unknown. 2 caps BID 27 days	Recovered
6	4y/F	ALL	Allogeneic +70	Yes	78	Fever	*L. plantarum*	26.14	5	Yes	ESBL	Yes	Yes	No	Yes	Yes	No	No	No	Penicillin, 10 days	Unknown. 2 caps BID 54 days	Recovered

Note. M, male; F, female; SCID, severe combined immune deficiency; ALL, acute lymphoblastic leukemia; NB, neuroblastoma; AML, acute myeloblastic leukemia; MBI-LCBI, mucosal barrier injury laboratory confirmed bloodstream infection; MDRO, multidrug-resistant organism; CRE, carbapenem-resistant Enterobacterales; ESBL, extended spectrum β-lactamase; GVHD, graft-versus-host disease; ICU, intensive care unit; CVC, central venous catheter; QD, once daily; BID, twice daily.

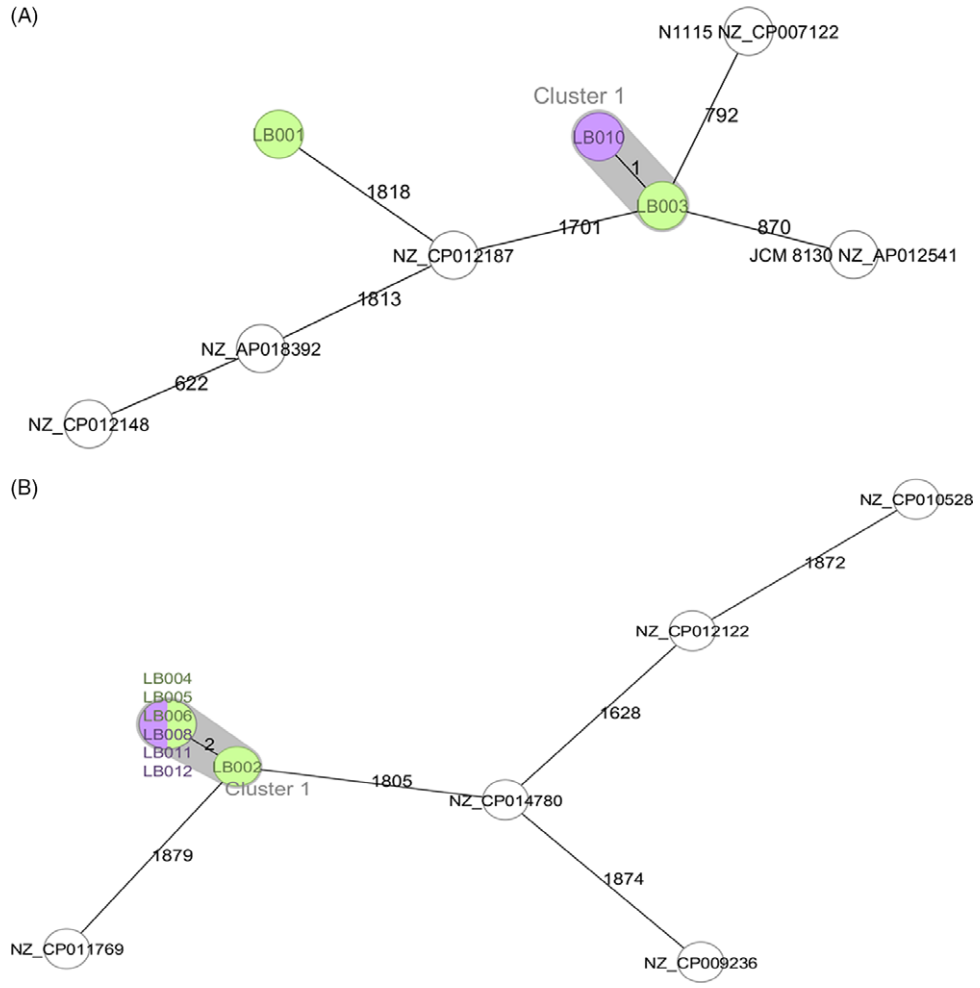

Fig. 1. Minimum spanning trees for lactobacillus isolates sequenced by core genome multilocus sequence type. Green circles represent probiotic isolates. Purple circles represent patient blood isolates. White circles are NCBI reference isolates. Line numbers represent distance (number of alleles difference) between the isolate and its nearest neighbor. Isolates with less than 20 alleles difference from nearest neighbor are considered related. (A) *Lactobacillus paracasei* and (B) *L. plantarum.*

Since July 2018, 20%–80% of hospitalized HCT patients have used probiotics compared to none before then (Supplementary Fig. S2).

Table 1 lists patient characteristics. The median age was 4 years (range, 0.8–16). Patients were at median day +41 (range, 6–103) after transplant and developed *Lactobacillus* bacteremia at median hospital day 20 (range 3–78). Upon review of common exposures, including shared personnel, medications, locations, equipment, and products, probiotics have been administered in all cases. Also 3 patients (2.35 per 1,000 patient days) used probiotics for MDRO colonization, and 2 patients (1.57 per 1000 patient days) used probiotics for both MDRO colonization and gut GVHD, and 1 patient had no clear indication for probiotics. None of the cluster patients had gut GVHD as the only indication for probiotic use. None of the *Lactobacillus* bacteremia cases before August 2019 had received probiotics, and only 1 patient was an HCT recipient (data not shown).

Patients 1, 2, and 3 received probiotic product 1. It was unclear which product the other 3 patients received. Six probiotic *Lactobacillus* isolates (LB001 and LB002 from product 1, LB003 and LB004 from product 2, and LB005 and LB006 from patient 5 supply) and 5 blood *Lactobacillus* isolates (LB008 to LB012 from patients 2 to 6, respectively) were analyzed. The isolate from patient 1 was not available. Only 2 *Lactobacillus* spp (*L. plantarum* and *L. paracasei*) were isolated from probiotics. Sequencing of *L. paracasei* isolate from LB005 recategorized it as *L. plantarum*. Isolate LB009 was identified as *L. rhamnosus* and was not included in the analysis.

Two trees for relatedness were created (Fig. 1A and 1B). Of *L. paracasei* isolates, LB003 and LB010 differed by 1 allele. LB001 was unrelated (Fig. 1A). Of *L. plantarum* isolates, LB008, LB011, and LB012 were identical to LB004, LB005, and LB006, and all were closely related to LB002 (Fig. 1B). Furthermore, *Lactobacillus* isolates from patients 2, 5, and 6 were proven to be related to products 1 or 2, and an isolate from patient 4 to was related to product 2.

Discussion

We report a cluster of *Lactobacillus* bacteremia related to probiotic use in pediatric HCT recipients. Probiotics generally contain 10^6 CFU per gram of viable organisms, but the probiotic dose required for clinical effects have not been not well established.[2,3] Also, significant differences in bacterial viability, activity, purity, and composition may exist among preparations because probiotics, in contrast to drug requirements, are marketed as dietary

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supplements and do not undergo premarket safety review by the US Food and Drug Administration.[4]

Although our investigation provided evidence for relatedness of the clinical to probiotic *Lactobacillus* isolates, it did not confirm the mechanism of bacteremia. We present 3 potential explanations. First, all cluster patients had compromised mucosal barrier integrity due to diarrhea, mucositis, neutropenia, or gut GVHD. Therefore, translocation of the probiotic *Lactobacillus* from the injured gut mucosa to bloodstream is a likely mechanism in immunocompromised patients. The second hypothesized mechanism is potential central venous catheter (CVC) contamination at the time of probiotic administration. A probiotic supplement taken by a hospitalized patient have been reported the source of *S. boulardii* sepsis in neighboring patients who had not received the supplement, possibly due to contamination of vascular catheters.[5] A third potential mechanism for *Lactobacillus* bacteremia is CVC contamination with stool which was the likely explanation in patient 1. Most cases of reported probiotics-related infections have resolved with appropriate antimicrobial therapy.[6–9] *Lactobacillus* spp was reported as the most common cause of bacteremia among HCT recipients taking probiotics, mostly occurring before day+100.[10] However, there was no attributable mortality in that study, similar to our findings. The use of the probiotic product in hospitalized HCT patients in our center was discontinued after this investigation.

This study had several limitations. This study provided evidence for probiotics being the source of *Lactobacillus* bacteremia in HCT recipients. However, the mechanism for positive blood cultures remains speculative. We described a case series but did not include controls. A retrospective cohort study of HCT recipients is ongoing at our center to evaluate the incidence and relative risk for *Lactobacillus* infections. Also, the probiotic product received by 3 patients could not be specified by record review and sequencing.

In summary, we describe a cluster of pediatric HCT recipients with *Lactobacillus* bacteremia with genomic evidence of relatedness to their use of probiotics. Well-designed clinical trials and robust oversight of the probiotic manufacturing process are needed to evaluate the safety of probiotic use in transplant recipients and other immunocompromised patients. Until these data become available, use of probiotics in immunocompromised patients should be avoided.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2021.515

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