When good bacteria go bad: New links between bacteremia and probiotic use

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Table 1. Detailed clinical information on five cases

No.	1	2	3	4	5
Age (y.o.)	68	81	77	53	19
Sex	female	female	male	male	female
Onset during hospitalization	yes	yes	yes	yes	yes
Diseases requiring hospitalization	Chemotherapy	Immunosuppressive treatment	post aortic valve replacement	Simultaneous pancreas and kidney transplantation	Double lung transplantation
Underlying disease	Esophageal cancer / Gastric cancer	Dermatomyositis	Aortic valve regurgitation, End-stage kidney disease	End-stage kidney disease, Type 1 diabetes	Idiopathic pulmonary arterial hypertension
Immunosuppression	yes	yes	no	yes	yes
Charlson Comorbidity Index	2	1	4	6	1
Central venous catheter insertion	yes	no	yes	no	yes
Concurrent MIYA-BM® use	Yes	No (but previously administered another probiotic with *C. butyricum*)	Yes	Yes	Yes
Appropriate reason for the prescription of probiotics	Yes (concomitant antibiotic use)	N/A	Yes (concomitant antibiotic use)	No	No
Duration of use of probiotics (Days)	8	N/A	12	91	30
polymicrobial bacteremia	yes (MSSA)	yes (*E. faecium*/MRCNS)	none	none	none
Symptoms of onset	Fever and diarrhea	Fever and diarrhea	Fever and abdominal pain, septic shock	Fever and abdominal pain	Fever and diarrhea
Diagnosis	Enterocolitis	Enterocolitis	NOMI	Duodenal perforation	Enterocolitis
Antibiotics	CMZ	CTRX	MEPM	MEPM	VCM
90-day mortality	alive	alive	**died**	alive	alive

Abbreviations: MSSA; Methicillin-Resistant *Staphylococcus aureus*, E. faecium: *Enterococcus faecium*, MRCNS; Methicillin-resistant coagulase-negative Staphylococci, NOMI; non-occlusive mesenteric ischemia, CMZ; cefmetazole, CTRX; ceftriaxone, MEPM; meropenem, VCM; vancomycin, N/A; not applicable.

Detailed clinical information on five cases. Credit: Osaka University

Probiotics offer a range of health benefits, but their adverse effects can

occasionally lead to bacteremia, wherein bacteria circulate in the bloodstream throughout the body. In Japan, Clostridium butyricum (C. butyricum) MIYAIRI 588 is commonly used, yet the prevalence and characteristics of bacteremia caused by this strain, as well as its bacteriological and genetic profile, remain unknown.

A research team from the Graduate School of Medicine, Osaka University, found an association between bacteremia and probiotics from a study of the genetic materials of bacteria in hospitalized patients with bacteremia. The study is published in the journal *Emerging Infectious Diseases*.

From September 2011 to February 2023, Osaka University Hospital documented 6,576 cases of positive blood cultures. Among these, C. butyricum was detected in five cases (0.08%).

Table 2. Antibiotic susceptibility of each clinical bacterial strain and three medicinal strains

Patient No.	1	2	3	4	5	Medicinal strains of CBM588		
Strain no.	114-4	129-32	180-11	181-16	216-41	No.1	No.2	No.3
C. butyricum MIYAIRI 588	MIC (mg/L)							
Penicillin	0.25	0.25	0.5	0.5	0.25	0.25	0.25	0.25
Ampicillin	0.25	0.25	0.25	0.25	0.25	0.12	0.25	0.25
Cefotaxime	32	32	32	32	32	32	32	32
Ceftriaxone	8	8	16	8	16	8	16	8
Cefmetazole	≤4	≤4	8	≤4	≤4	≤4	≤4	≤4
Imipenem	1	1	2	1	1	1	1	1
Meropenem	≤0.12	≤0.12	0.5	≤0.12	≤0.12	≤0.12	≤0.12	≤0.12
Sulbactam/ampicillin	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
Clavulanic acid/Amoxicillin	0.25	0.25	0.5	0.25	0.25	0.12	0.25	0.12
Tazobactam/Piperacillin	≤8	≤8	≤8	≤8	≤8	≤8	≤8	≤8
Clindamycin	0.5	0.25	0.5	0.5	0.25	0.25	0.5	0.25
Moxifloxacin	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5
Metronidazole	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2

Antibiotic susceptibility of each clinical bacterial strain and three medicinal strains. Credit: Osaka University

Table 3. Results of whole-genome sequencing of *Clostridium butyricum* obtained from blood culture

Patient no.	1	2	3	4	5
Strain no.	114-4	129-32	180-11	181-16	216-41
Average nucleotide identity (ANI)* against CBM 588 strains	99.986	99.947	99.949	99.943	99.946
All variants†‡	50	40	63	65	81
variants not on rRNA region‡	19	1	2	1	0

*ANI were calculated using FastANI (*31*)
†Number of all variants in coding genes, which were called and annotated by GATK HaplotypeCaller (*32*) and snpEff (*33*) with annotation information from DFAST (*34*).
‡Number of variants after excluding variants on rRNA region.

Results of whole-genome sequencing of Clostridium butyricum obtained from blood culture. Credit: Osaka University

Whole-genome sequencing revealed that all five strains of C. butyricum-causing bacteremia were derived from probiotics. In two of these cases, no clear reason for appropriate oral intake of the probiotics could be identified, and one patient died within 90 days after the bacteremia diagnosis.

"Probiotics can provide a variety of health benefits, but this study shows that even such agents can present with rare but serious adverse events," says study lead author Ryuichi Minoda Sada.

"Our findings underscore the risk for bacteremia resulting from probiotic use, especially in hospitalized patients, necessitating judicious prescription practices."

It is expected that the results of this study will increase awareness of the potential health risks associated with probiotics. It is recommended to avoid aimless and unnecessary prescribing of probiotics, especially in hospitalized patients undergoing immunosuppressive treatment.

More information: Ryuichi Minoda Sada et al, Clostridium butyricum Bacteremia Associated with Probiotic Use, Japan, *Emerging Infectious Diseases* (2024). DOI: 10.3201/eid3004.231633

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