

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

May 2 2024

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 <i>C. butyricum</i>) | 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 (<i>E. faecium</i> /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 |
| <i>C. butyricum</i> 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 ^{† i} | 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](https://doi.org/10.3201/eid3004.231633)

Provided by Osaka University

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