Good bacteria gone awry: probiotic-induced bacteremia in a vulnerable patient - a unique case report

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Abstract

Probiotics have gained immense popularity as an over-the-counter supplement in recent years. Many people use probiotics to promote gastrointestinal and immunologic health. However, there is not much concrete evidence regarding the safety and efficacy of these ingested capsules of foreign bacterial content and their potential to become opportunistic pathogens. Special populations, such as immunocompromised patients, may try these supplements for their touted benefits and the label of being naturally occurring, but they can unknowingly cause undue harm to their health. Probiotics are unregulated supplements that cannot definitively claim to be the appropriate mixture of bacteria for diverse gut microbiomes, confirm the optimal dosage before adverse events are observed, or provide a number needed to harm as seen in other medical trials. Here, we present a case of a 69-year-old female with multiple comorbidities who presented with weakness and was found to have lactobacillus bacteremia due to bacterial translocation of pathogens introduced through probiotic consumption. This incident highlights the increasing need for investigation regarding unregulated over-the-counter supplements, specifically probiotics, and their utility and safety. Along with emerging data regarding probiotics and their beneficial but sometimes harmful impact, our case aims to create a dialogue about when the use of adjuvants is appropriate and within which patient populations.

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Background

In recent years, probiotic supplements have grown in popularity for perceived gastrointestinal and immune benefits. While generally considered as a safe product to use, probiotics pose a potential risk for increased adverse events among the immunocompromised. One of the rare, but potentially life threatening side effects of their use is translocation from the gut and into the blood stream where they can cause systemic infection, or bacteremia.[1] As probiotics are regulated as a food and not a therapeutic medication or supplement, their safety profile and potential adverse effects have come under significant scrutiny, with some denoting increased invasive infections in critical care patients.[2] Moreover, some case reports have demonstrated that certain species common to probiotic supplementation can often act like an opportunistic pathogen and infect the individual if they are constitutionally compromised.[3]

Due to the societal shift to more naturopathic and alternative treatments in clinical practice, it is important to explore the potential repercussions of wanton probiotic use. Recently, a review on probiotic safety emphasized the importance of strict regulatory frameworks and implementation of more rigid clinical guidelines to reduce the incidence of probiotic-induced bacteremia.[4] Moreover, it was believed that the use of probiotics during a course of antibiotic therapy offered the potential to mitigate disruptions to the normal gut flora in the already compromised patient. However, a recent systematic review examining antibiotic-induced dysbiosis found no benefit to the practice, and depicted

no impactful protection afforded, while potentially exposing the individuals with weakened immune systems to potential harm from translocating probiotic supplement species.[5] These findings challenge the routine and unsupervised utilization of probiotic supplementations, further highlighting a need for stricter oversight in their therapeutic employment.

Case Report

A 69-year-old female with a past medical history of fibromyalgia with increasing disability over the last 25 years, depression, diabetes mellitus, hyperlipidemia, hypertension, current tobacco smoker and obesity presented to the Emergency Room for evaluation of progressive confusion over the last few weeks. She took all her medications as recommended for her existing comorbidities along with a daily probiotic that she felt enhanced her holistic wellness. The family at bedside provided collateral history highlighting that the patient had fallen and hit her head in the shower a few weeks ago. At time of injury, a Computerized Tomography (CT) without contrast of her head showed no acute findings. Although, since her fall, she experienced difficulty ambulating with more than four additional falls, and episodes of urinary incontinence. Three days prior to her Emergency Room (ER) visit, the patient had rapidly evolving symptoms of disorientation and forgetfulness.

Evaluation in the ER noted a D-dimer level of 1,684, leukocytosis at 17,000, glucose at 219, potassium at 5.2, and lactic acid at 3.0. A urinalysis indicated glucose levels greater than 500. The viral respiratory panel and COVID tests returned negative results while blood cultures were positive for Gram-positive cocci in clusters. A non-contrast CT scan of the head showed no acute abnormalities, while a Chest Radiograph (CXR) revealed bilateral patchy airspace disease. The patient was admitted for acute metabolic encephalopathy from possible pneumonia and suspected bacteremia and received maintenance IV fluids, started on IV zosyn 3.375 g every 8 hours and IV vancomycin 15 mg every 24 hours. She was unable to obtain a Magnetic Resonance Imaging (MRI) without contrast of her brain due to a noncompliant vagal nerve stimulator implant. A repeat CT head without contrast was done for persistent altered mental status and returned unremarkable which led to further suspicion that her symptoms were due to an infectious etiology. Thus, the patient remained on empiric antibiotics coverage.

Soon after, blood cultures returned positive for *Staphylococcus hominis*, considered a contaminant, followed by *Lactobacillus grasseri*. Given the lactobacillus species is uncommon pathogens in suspected bacteremia, it was most likely introduced into her bloodstream from her probiotic supplement containing this species. With positive blood cultures providing direction on how to best tailor her antibiotics, the patient's treatment was adjusted based on the antibiogram. Over time, the patient's mentation improved and she became more oriented. At the time of discharge, the patient remained afebrile and hemodynamically stable. She was discharged on an oral antibiotic course of amoxicillin 500 mg TID 10-day course with the recommendation to closely follow-up with her primary care physician and to be more vigilant of the over-the-counter supplements she uses.

Discussion

This case highlights the importance of judicial probiotic usage in patients who may be susceptible to opportunistic translocation from the gut to the bloodstream. Empiric antibiotic treatment covered the patient's supplement-induced pathogen, but would not have been needed if appropriate physician and patient education

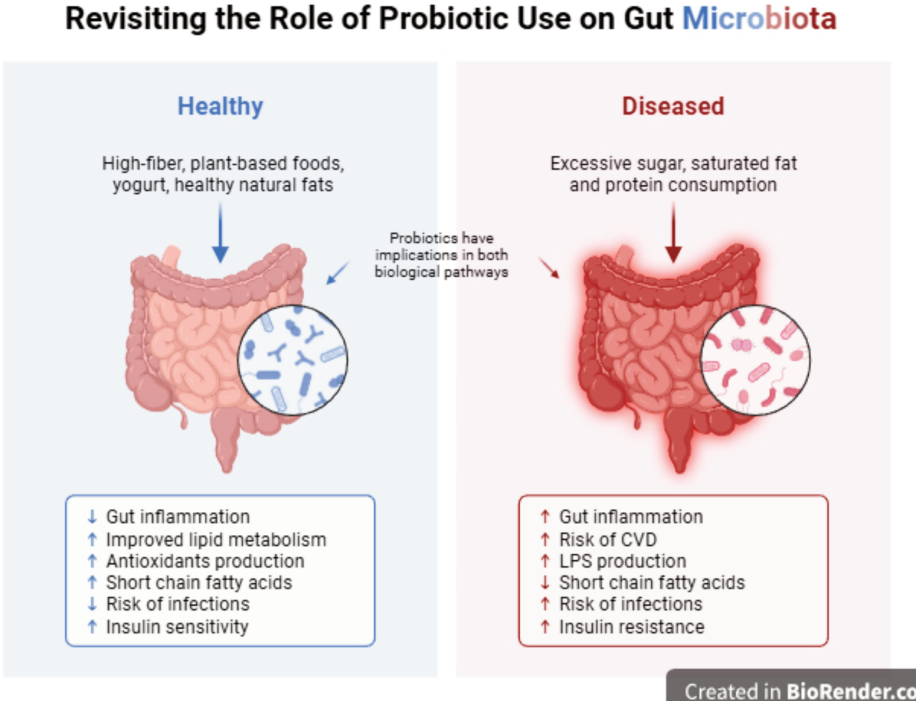

Figure 1. Central illustration depicting the cascade effects in probiotic modulation of gut microbiome.

was provided. Probiotics are currently regulated as a food, not as potential therapeutics, but these classifications may need to be re-evaluated on a wider scale given the growing body of evidence refuting their safety profiles specifically in immunocompromised patients. However, the authors of one clinical study published by the Infectious Diseases Society of America (IDSA) speculated that infections were likely due to disruption of mucosal barriers or potential cross-contamination of central venous catheters in immunocompromised patients receiving probiotics. Although the mechanism by which probiotics (specifically lactobacillus species) translocate into the blood and cause bacteremia is not fully understood, it is believed that the gut wall-adherence properties of probiotics, lack of platelet aggregation to the probiotic species, and having compromises to the bloodstream (central venous catheters) or gut-wall can predispose one to probiotic bacteremia.[1]

Furthermore, certain comorbid conditions can also predispose individuals to probiotic-induced bacteremia. In a retrospective case series, the authors investigated a cluster of *Lactobacillus* bacteremia in pediatric Hematopoietic Cell Transplant (HCT) recipients and its potential relation to probiotic use. In July 2018, probiotic use was approved for HCT patients who had Gut Graft-*Vs*-Host Disease (gGVHD), *C. difficile* infection, or colonization with multidrug-resistant organisms. During the 4-month time period, 34 hospitalized HCT patients received at least one day of probiotics; of those patients, six (17.6%) were subsequently bacteremic with *Lactobacillus*. In those who developed bacteremia, three patients had Multidrug-Resistant Organisms (MDRO) colonization, two patients had both MDRO colonization and gGVHD, and one had no indication for probiotic use.[6] In a separate study, researchers compared the effects of probiotics and Autologous Fecal Microbiota Transplantation (a-FMT) on post-antibiotic gut mucosal microbiome. They found that contrary to homeostasis, antibiotic perturbation enhanced probiotics colonization in the human mucosa. Compared to spontaneous post-antibiotic recovery, probiotics induced a markedly delayed and persistently incomplete indigenous stool/mucosal microbiome reconstitution and host transcriptome recovery toward homeostatic configuration, while a-FMT induced a rapid and near-complete recovery within days of administration. *In vitro*, Lactobacillus-secreted soluble factors contributed to probiotics-induced microbiome inhibition. Collectively, potential post-antibiotic probiotic benefits may be offset by a compromised gut mucosal recovery.[7] A recent article in the Journal of Clinical Nutrition also highlights concerns about the safety of probiotics, particularly lactic acid bacteria, and bifidobacteria, in light of their isolation from clinical infections. While probiotics are generally considered safe for healthy individuals, their role in opportunistic infections in immunocompromised patients is a concern. Factors such as chronic diseases, mucosal injury, and drug-induced abnormalities increase the risk of bacterial translocation, which may result in infections in vulnerable populations (Figure 1).[8] The treatment of Lactobacillus Bacteremia (LB) should be based on the clinical presentation and antibiotic susceptibility testing, as *Lactobacillus* spp. show variable susceptibility to antibiotics. Goldstein *et al.* analyzed the antibiotic susceptibility of commonly isolated human lactobacilli by species.[9] They concluded that it is not possible to predict or provide specific treatment recommendations for individual species or strains. Susceptibility studies of Lactobacilli have varied widely in sources, methodologies, culture conditions, and breakpoints, making standardization challenging. Notably, some *Lactobacillus* spp. are intrinsically resistant to vancomycin and aminoglycosides, while other glycopeptides show variable activity.[1] Lactobacilli isolated from patient samples are often considered contaminants, and antibiotics are usually not given. However, careful evaluation of the patient's symptoms, obtaining a comprehensive history, including medication reconciliations, and a thorough laboratory workup are crucial to confirm infection.

Conclusions

Screening with blood cultures is integral to this process and should be used to guide effective treatment modalities. These results should be taken into account with specific scenarios and patient populations, given the strong unlikelihood of LB manifesting in immunocompetent patients. Adequately treating any underlying etiologies that may be adversely contributing to a patient's immunocompromised state is also important. Due to the challenges in Lactobacillus species identification, susceptibility testing, and the rarity of these infections, clinical experience and trials on optimal antibiotic treatments are limited. Commonly used antibiotics include penicillins (penicillin and ampicillin), with or without aminoglycosides, and cephalosporins.[1,10] This case report aims to contribute to the growing body of literature advocating the more prudent use of probiotics, particularly among high-risk populations. By documenting and analyzing this unique case of LB, we aim to emphasize the importance of judicious and evidence-based probiotic use.

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