Original Article

Lactobacillus rhamnosus Infection: A Single-center 4-year Descriptive Analysis

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Abstract

Introduction: *Lactobacillus rhamnosus* is an anaerobic or facultative anaerobic Gram-positive rod that is commonly found in the human gastrointestinal tract and vaginal tract. Infections secondary to *L. rhamnosus* have not been well illustrated in the literature. The purpose of this study was to describe the clinical courses of patients with *L. rhamnosus* infection in our institution. **Materials and Methods:** A retrospective chart review was performed on patients with the growth of *L. rhamnosus or L. rhamnosus/casei* from January 1, 2013, to December 31, 2017. **Results:** Forty-seven patients had growth of *L. rhamnosus or L. rhamnosus/casei.* Of these, 35 patients were included in the study who received therapy. Twenty patients (57.1%) presented with leukocytosis, 17 (48.5%) with fever, and 15 (42.8%) with abdominal pain. Twenty-three (66.1%) had intra-abdominal infection, 8 (22.3%) were bacteremic, and 4 (11.4%) had mediastinitis. Thirty-three patients (94.3%) had a polymicrobial infection. Eighteen (51.4%) patients had disruption of the gastrointestinal tract, 14 (40.0%) had underlying malignancy, and 11 (31.4%) had prior antibiotic exposure. Twenty (57.1%) patients clinically improved after therapy. However, the overall mortality rate was 56.2%, all of whom died of unrelated causes. **Conclusion:** *Lactobacilli* are organisms thought to have low pathogenicity. Our study identified cases of *L. rhamnosus* infections in a population of patients with serious underlying medical conditions.

Keywords: Anaerobic infections, Lactobacillus rhamnosus, Lactobacillus rhamnosus/casei, Lactobacillus, polymicrobial infections

Introduction

Lactobacilli are anaerobic or facultative anaerobic Gram-positive rods that are ubiquitous microorganisms colonizing the human gastro-intestinal and female genitourinary tracts.[1] They are not considered commensals of the skin. When isolated in clinical specimens, *Lactobacilli* are often considered as contaminants due to their low virulence; however, this group of bacteria has progressively been noted to cause significant infections in both immunocompetent and immunocompromised patients.[2] The most common disease processes caused by *Lactobacilli* are endocarditis and bacteremia.[3-5] Several studies have shown increasing rates of *Lactobacillus* bacteremia due to widespread use of probiotics.[6,7] Other clinical presentations of *Lactobacillus* infection include intra-abdominal infection, septic arthritis, urinary tract infection, pneumonia, meningitis, and endometritis.[8-13] The leading causative strains of infection are *Lactobacillus casei* and *Lactobacillus rhamnosus*.[14] Infections caused by *L. rhamnosus* are not well described in the literature. In our institution, we have recently encountered several significant infections secondary to *L. rhamnosus.* From February 2016 to July 2017 alone, there have been over 40 isolates of *L. rhamnosus* from different sites including blood, urine, wound, abdominal abscess, and sputum. The purpose of this study is to characterize invasive isolates of *L. rhamnosus* at our facility, identify risk factors and outcomes associated with the infection, and finally, to describe how these infections were managed by our providers.

Materials and Methods

Cases were identified by reviewing the culture reports of patients ≥18 years who were positive for *L. rhamnosus* or *L.*

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rhamnosus/*casei* over a 4-year period (January 1, 2014, to December 31, 2017) from the microbiology records of Loyola University Medical Center (LUMC), a quaternary care facility with 547 licensed beds in IL, USA. Patients with confirmed infections secondary to *L. rhamnosus or L. rhamnosus*/*casei* who received treatment were included in the study. Patients with a positive culture who did not receive treatment were excluded from the study. The clinical records of each of these patients were reviewed. Data collected included age, sex, specimen collected, date of collection, clinical presentation, diagnosis, underlying comorbidities including potential predisposing factors, other organisms isolated, antibiotic regimen, duration of therapy, source control method, and outcomes.

Prior to July 1, 2015, identification to the species level was determined using phenotypic methods including Gram stain, catalase reaction, and the AnIdent anaerobe identification system (bioMeriuex, Hazelwood, MO). After July 1, 2015, identification to the species level was determined using matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry using the Bruker MALDI Biotyper (Bruker Corporation, Billerica, MA), and the research used only database library. Our facility's methods could not differentiate between *L. rhamnosus* and *L. casei* in 12 of our cases; thus, the results were reported as *L.* rhamnosus/*casei.* Susceptibility testing was by broth microdilution methods.

Patient demographics and clinical characteristics were presented for all included patients and summarized for the sample as means and standard deviations for continuous variables and counts and percentages for nominal variables. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics and predisposing factors

A total of 47 patients who had growth of *L. rhamnosus* or *L. rhamnosus*/*casei* from different types of specimen were reviewed. The specimens collected were blood, abdominal fluid, abscess, pleural fluid, bronchial fluid, urine, and sputum. Of these 47 patients, 35 patients received treatment and thus were included in the study. The demographics and clinical characteristics of these patients are summarized in Tables 1 and 2. All patients identified were inpatients at the time of the diagnosis. The mean age was 63.8 ± 14.4 years, 14 (40.0%) patients were at least 70 years old, and 13 (37.1%) were younger than 60 years. About half of our cases were female. The three most common presenting features were leukocytosis, fever, and abdominal pain. Among those with leukocytosis, the mean white blood cell count was 16.7 ± 4.7. Twenty-three patients (65.7%) had intra-abdominal infection. Of these cases, 8 had viscus perforation and 7 had a history of fistulous communications. Four patients had mediastinitis and all of these cases either had esophageal perforation or fistulous tracts. Eight patients (22.9%) had *Lactobacillus* bacteremia and all but one of these cases had associated

Table 1: Patient demographics

	Overall (*n*=35) patients, *n* (%)
Age (years), mean±SD	63.8±14.4
Age (years)	
<60	13 (37.1)
60-69	8 (22.9)
≥70	14 (40.0)
Female	19 (54.3)
Comorbidities/conditions	
GI tract disruption	18 (51.4)
GI-related procedures	17 (48.6)
Malignancy	14 (40.0)
Prior antibiotic exposure	11 (31.4)
Other procedures	8 (22.9)
Cardiovascular disease	7 (20.0)
Immunosuppression	6 (17.1)
Biliary disease	4 (11.4)
Diabetes mellitus	3 (8.6)
Renal disease	1 (2.9)

GI: Gastrointestinal, SD: Standard deviation

Table 2: Clinical characteristics

	Overall (*n*=35) patients, *n* (%)
Clinical presentation	
Leukocytosis	20 (57.1)
Fever	17 (48.6)
Abdominal pain	(42.9)
Hypotension	7 (20.0)
Tachycardia	6 (17.1)
Respiratory symptoms	4 (11.4)
Others (facial swelling, fatigue, chills, and diarrhea)	5 (14.2)
Specimen collected	
Abdominal fluid	16 (45.7)
Blood	9 (25.7)
Pleural fluid	4 (11.4)
Others (abscess, wound, tissue, and other fluids)	6 (17.1)
Diagnosis	
Intra-abdominal infection	23 (65.7))
Bacteremia	8 (22.9)
Mediastinitis	4 (11.4)
Others (empyema, septic arthritis, pneumonia, vascular graft infection, and mandibular abscess)	7 (20.0)
L. rhamnosus	23 (65.7)
L. rhamnosus/casei	12 (34.3)
Other organisms isolated	
Candida sp.	19 (54.3)
Enterococcal sp.	19 (54.3)
Anaerobes	17 (48.6)
Enterobacteriaceae	15 (42.9)
Streptococcal sp.	11 (31.4)
Other Gram-positive organisms	9 (25.7)
Other Gram-negative organisms	4 (11.4)

L. rhamnosus: *Lactobacillus rhamnosus*

gastrointestinal tract abnormalities or recent invasive gastrointestinal procedure. The most important risk factor noted in this study was the disruption of the gastrointestinal tract, such as viscus perforation and fistulous tract formation, gastrointestinal-related procedures, malignancy, and prior antibiotic use. The most common prior antibiotic therapies received were vancomycin and cephalosporins.

Microbiological findings

Twenty-three patients (65.7%) had *L. rhamnosus,* and 12 (34.3%) had *L.* rhamnosus/*casei.* Almost half of our specimens were collected from the abdominal fluid. All patients had polymicrobial infections except in two cases. The most common coinfection was secondary to *Candida* species and *Enterococcal* followed by anaerobic organisms, enterobacteriaceae, and *Streptococcal* species.

Susceptibility testing was performed in only two patients with bacteremia by broth microdilution methods in our facility. Another patient with bacteremia had susceptibility testing done at an outside facility prior to transfer to Loyola University Medical Center (LUMC). The method of susceptibility testing for this patient was unknown.

Management of infection

All but two of the included patients in our study had polymicrobial infection. Therefore, these patients received broad-spectrum therapy. The most common agents used were vancomycin (n = 17), metronidazole (n = 16), carbapenems (n = 15), piperacillin-tazobactam (n = 12), and cephalosporins (n = 9) [Table 3]. Two patients with no other organisms isolated, however, still received broad-spectrum therapy due to the nature of their infection and underlying conditions. One patient had gastric perforation, and another had a history of acute myelocytic leukemia and was thought to have aspiration pneumonia.

For those who completed active therapy, the mean duration was 3.7 ± 2.2 weeks. One patient was transferred to a different facility while on therapy, so the duration of therapy was unknown. Four patients were placed on chronic suppression due to poor source control, but two of these patients were lost to follow-up and one went into hospice care. One patient remained on chronic active therapy due to persistent abscesses on imaging.

Source control measures were undertaken in 25 patients (71%). Source control is defined as a process of controlling the source of infection to reestablish optimal function.[15] The most common method of source control was percutaneous drainage and was performed in 45.7% of our patients.

Outcomes

The outcomes were measured in terms of clinical improvement and survival, as shown in Table 4. Twenty of our patients (57.1%) clinically improved after therapy. Nine patients (26%) died during the hospitalization when *Lactobacillus* infection was established. All but one of these cases went into hospice or had withdrawal of care as requested by their families. All of these patients had significant underlying medical conditions including malignancy, chronic liver disease, chronic renal failure, and gastrointestinal abnormalities, such as enteric fistulas and bowel perforation. Five patients (14.3%) had recurrence of their infection based on clinical and radiographic evidence. However, only one of these patients had re-isolation of *L. rhamnosus*. Three patients were lost to follow-up. At 1-year follow-up, 56.2% of our patients with *L. rhamnosus or L. rhamnosus*/*casei* infection had died (18 of 32 patients with available 1-year follow-up data). All died of unrelated causes.

Table 3: Management of infection

	n (%)
Antibiotic therapy	
Vancomycin	17 (48.6)
Metronidazole	16 (45.7)
Carbapenems	15 (42.9)
Piperacillin-tazobactam	12 (34.3)
Cephalosporins	9 (25.7)
Others (daptomycin, linezolid, clindamycin, trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, aztreonam, fluoroquinolones, and ampicillin-sulbactam)	15 (42.9)
Status of therapy	
Completed	20 (57.1)
Not completed	9 (25.7)
On-going therapy	1 (2.9)
Chronic suppression	4 (11.4)
Unknown/loss to follow-up	3 (8.6)
Source control	
Percutaneous drainage	16 (45.7)
Surgical evacuation/resection/repair/debridement	11 (31.4)
Removal of infected line/catheter	2 (5.7)
None	10 (28.6)

Table 4: Outcome

	n (%)
Clinical improvement	20 (57.1)
Reinfection	5 (14.3)
Mortality	
Inhospital	9 (25.7)
1-year follow-up	18/32 (56.2)
Loss to follow-up	3 (8.6)

Discussion

L. rhamnosus has been reported as a cause of significant bacteremia in both immunocompetent and immunocompromised patients.[2,5,16] Some infections may be undiagnosed due to poor culture technique and lack of proper identification.[17] Harty *et al*. studied the potential pathogenicity of *Lactobacillus* sp. in infective endocarditis cases. Identified cases predominantly belonged to *L. rhamnosus* and *L. paracasei* subspecies, suggesting a greater pathogenic potential compared to other species.[18] This study concluded that due to their ability to

aggregate platelets and bind to fibronectin, fibrinogen and collagen provide evidence to their pathogenicity.[18]

We reviewed 35 cases of *L. rhamnosus* infections at our institution over a period of 4 years. Thirty-three of our patients had polymicrobial infections and more than half had disruption of the gastrointestinal tract. Other prevalent characteristics identified in our study are malignancy, prior antibiotic use, and recent surgical procedures.

Historically, treatment of *Lactobacillus* infection consisted of high-dose penicillin and an aminoglycoside for synergy.[8,19] Other studies have also described nontraditional therapy for *L. rhamnosus* infection that comprised of broad-spectrum agents such as cephalosporins, carbapenems, aminopenicillins, and lincomycin.[5,9,16] Several studies showed that vancomycin demonstrated a high level of resistance.[20-22] However, a study by Cannon *et al*. showed that 22.5% of the *Lactobacillus* isolates were sensitive to vancomycin, and these were either *L. acidophilus* or unspeciated.[14] Due to this varying susceptibility pattern, treatment of *Lactobacillus* infection, especially lactobacillemia, should be in accordance to the pathogenic potential of the *Lactobacillus* strain and susceptibility testing.[2] Many microbiology laboratories, however, currently do not perform routine susceptibility testing on *Lactobacillus* species and therefore may not have standardized panels that can be interpreted or compared between institutions or even patient to patient at the same institution. Therefore, we would recommend case-by-case *Lactobacillus* susceptibility testing when there is a concern for the pathogenic involvement of the *Lactobacillus* strain. In this present study, none of the patients were treated with the traditional recommended regimen and our clinical data were collected retrospectively; therefore, we cannot provide recommendations as to which therapy should be selected for adequate treatment of *Lactobacillus* infections.

Our study confirms the conclusion of previous studies that *Lactobacilli* exhibit a low level of pathogenicity.[3,4] More than half of our patients were cured or had clinical improvement after therapy. Eighteen patients died, but no deaths were attributed to *Lactobacillus* infection, and all had significant underlying medical conditions accounting for the high mortality rate in our patient population. Several studies also showed similar data, concluding that the presence of *Lactobacillus,* specifically lactobacillemia*,* was associated with worse survival.[3,14]

Our study has several limitations. First, this study was retrospective in nature, and therefore, we are unable to reliably draw conclusions regarding the efficacy of treatment. Second, the patient population all had polymicrobial infections, which limits our ability to analyze *Lactobacillus* infection independently. In addition, many of these patients had high morbidity and mortality related to their underlying medical conditions, which is a confounding factor in analyzing the significance of the presence of *Lactobacillus*. Finally, this study serves as a description of *Lactobacillus* infections but does not attempt to compare outcomes in patients who were treated for *Lactobacillus*, as compared to those who were not treated.

Conclusion

Lactobacillus colonizes the gastrointestinal tract and is involved in polymicrobial infections resulting from a gastrointestinal source. While *Lactobacillus* has traditionally been considered a low-virulence organism or a nonpathogenic contaminant, we provide a retrospective observational study that identified 35 cases of *L. rhamnosus* infection in critically ill patients with significant comorbidities and high rate of mortality. To date, however, the literature has been lacking in descriptive studies documenting the treatment and outcomes of *L. rhamnosus*. Here, we provide data regarding the specific treatment and outcomes for all patients treated for *L. rhamnosus* infections during a 4-year period at our facility. *Lactobacillus* is known to be intrinsically resistant to vancomycin, and we noted a broad variation in treatment. Further data from prospective studies are needed to provide recommendations on the optimal treatment of *L. rhamnosus.*

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Conflicts of interest

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