MAJOR ARTICLE

Lactobacillus Bacteremia, Clinical Significance, and Patient Outcome, with Special Focus on Probiotic *L. Rhamnosus* GG

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***Lactobacillus* bacteremia is a rare entity, and its clinical significance is poorly defined. We have reviewed the risk factors and outcome for 89 case patients with *Lactobacillus* bacteremia. Species characterization was done in 53% of the cases, revealing 25 *L. rhamnosus* strains and 22 other *Lactobacillus* species. In 11 cases, the strain was identical with the probiotic *L. rhamnosus* GG. In 82% of the cases, the patients had severe or fatal comorbidities. Predisposing factors to bacteremia were immunosuppression, prior prolonged hospitalization, and prior surgical interventions. No significant differences were observed in these predisposing factors or clinical features between patients with cases associated with the various *Lactobacillus* species, other than higher C-reactive protein values in patients with *L. rhamnosus* bacteremia. Mortality was 26% at 1 month and was 48% at 1 year. In multivariate analysis, severe underlying diseases were a significant predictor for mortality (odds ratio [OR], 15.8), whereas treatment with antimicrobials effective in vitro was associated with lower mortality (OR, 0.22). We conclude that lactobacilli in blood cultures are of clinical significance and that their susceptibility should guide decisions about antimicrobial treatment.**

Lactobacilli live as commensals in the human oral, gastrointestinal, and genitourinal tracts. They are gram-positive, microaerophilic, or facultatively anaerobic rods that ferment to yield lactic acid [1]. Bacteremia caused by lactobacilli is rare, and data on its clinical significance is based only on case reports or data in abstract form [2–6]. Risk factors related to *Lactobacillus* bacteremia include impaired host defenses and severe underlying diseases, as well as prior surgery and prolonged antibiotic therapy ineffective for lactobacilli [7–8]. Clinical features of *Lactobacillus* bacteremia range from asymptomatic to severe septicemia and may be combined with pneumonia, deep abdominal abscesses, or endocarditis [7,9–10]. *Lactobacillus* bacteremia might be underdiagnosed, because lactobacilli are cumbersome to culture and to identify, and, in many cases, they have been regarded as contaminants [1].

In case reports of bacteremia, several *Lactobacillus* species have been identified, but the 2 most common species have been *Lactobacillus casei* and *Lactobacillus rhamnosus*—both of which are also common in probiotic use. In an epidemiological study of *Lactobacillus* bacteremia in Finland, we did not find any correlation between the increased probiotic use of *L. rhamnosus* GG (ATCC 53103) and the incidence of *Lactobacillus* bacteremia during 1990–2000 [11]. However, the widespread use of immunosuppressive therapy and antimicrobial agents ineffective against lactobacilli might increase their importance as possible pathogens among

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patients more vulnerable to infections. Furthermore, case reports of clinical infections connected to prior probiotic intake have been published [12–13].

To evaluate the predisposing factors, clinical course, and treatment of bacteremia due to various *Lactobacillus* species, we reviewed the medical records of the patients from our earlier epidemiological study [11]. This identified 89 cases, which constitutes the largest collection of data on *Lactobacillus* bacteremia to date. In contrast to the cases described in many previous reports, these cases were collected nationwide and coincided with an increase in consumption of probiotic *L. rhamnosus* GG. Our study enables the comparison of clinical outcomes for patients infected with various *Lactobacillus* species, with special emphasis on *L. rhamnosus* GG.

METHODS

Collection of* Lactobacillus *isolates and identification of cases of infection. Between 1990 and 2000, we collected lactobacilli isolated from blood cultures at Helsinki University Central Hospital (HUCH) (serving southern Finland, with a population coverage of 1.3 million during the time period). In addition, data on *Lactobacillus* bacteremia cases detected through the nationwide mandatory reporting of all positive blood cultures in Finland (population, 5.2 million) were collected from October 1994 until the end of 2000 [11]. This identified a total of 119 blood cultures positive for *Lactobacillus* bacteremia. Of these, 11 cultures were excluded: 9 cultures of samples obtained postmortem by heart puncture, 1 culture of a sample obtained from a 2-year old child after prolonged resuscitation, and 1 culture of umbilical cord blood obtained from a healthy newborn. For the remaining 108 reported cases of *Lactobacillus* infection, isolates were either not stored or did not grow in 42 cases. Thus, 66 isolates were available to be characterized to the species level. Of these 66 isolates, 19 were determined to be microorganisms other than lactobacilli. The remaining 47 *Lactobacillus* isolates were identified to the species level. In addition, the medical records from the 42 cases for which there was no possibility to reconfirm and analyze the *Lactobacillus* isolates to the species level were retrieved; thus, a total of 89 case patients were included in the present study.

Identification of the isolates. The growth of the isolates, their preliminary biochemical characterization, the *L. rhamnosus* species–specific PCR used, and typing by PFGE have been described elsewhere [11]. Partial sequencing of 16S rDNA [14] or species-specific PCR for *L. casei* [15], *Lactobacillus fermentum* [16], *Lactobacillus gasseri*, and *Lactobacillus zeae* [17] were performed to identify the strains. The type strain of each species was used as a positive control in the respective species-specific PCR. The sequences were analyzed with the Blastn program (version 2.2.5) and named according to the species producing the best alignment score and having a sequence identity of 99%–100%. Isolates belonged to 7 different *Lactobacillus* species: 25 isolates were *L. rhamnosus,* 9 were *L. fermentum*, 7 were *L. casei*, 2 were *L. gasserii*, 2 were *L. jensenii*, 1 was *L. zeae*, and 1 was *L. sake*. Of the 25 *L. rhamnosus* isolates, 11 isolates were regarded as *L. rhamnosus* GG, as they had PFGE patterns that were identical to those of probiotic *L. rhamnosus* GG, with 4 different restriction enzymes, as described elsewhere [11].

Susceptibility testing of lactobacilli. MICs were determined for the following antimicrobial agents: penicillin G, ampicillin, cephalothin, cefuroxime, ceftriaxone, ciprofloxacin, clindamycin, erythromycin, doxycycline, imipenem, netilmycin, tobramycin, piperacillin-tazobactame, trimethoprim-sulfamethoxazole, and vancomycin. After 24-h of growth, colonies were suspended in saline to match the McFarland 0.5 turbidity standard. Wilkins-Chalgren agar (Oxoid) plates supplemented with 5% sheep blood were inoculated with a suspension of the bacterial isolate. Etest strips (AB Biodisk) were placed on the surface of the agar plates, and the plates were incubated in a microaerophilic atmosphere (CampyPak Plus, Becton Dickinson Microbiology Systems) at 37°C for 24 h [18]. MICs were read at the point of intersection between the elliptical zone of inhibition that developed and the test strip. The MICs were interpreted according to the recommendations of the NCCLS for bacterial isolates grown aerobically [19].

Review of patient data. Clinical data was retrieved in a blinded manner so that the reviewer was not aware of the microbiological data. Data obtained included age, sex, underlying diseases, and possible predisposing factors. Previous surgery, surgical drainage, endoscopic examinations, and urogenital or other invasive procedures—such as bronchoscopy or deep tissue biopsy—performed within 72 h prior to the onset of bacteremia were assessed. Two independent reviewers who were blinded to each other evaluated the severity of underlying diseases according to the classification of McCabe and Jackson [20], dividing the group of case patients into totally healthy patients (class 1), patients with mild underlying diseases (class 2), patients with ultimately fatal diseases (i.e., death expected within 5 years; class 3), or patients with rapidly fatal diseases (i.e., mortality expected within 6 months; class 4). In 38% of cases, the reviewers' classifications were discordant, and the classification was based on mutual agreement after discussion between them. Presence of endocarditis was noted according to Duke's criteria [21]. Receipt of immunosuppressive therapy within 30 days prior to onset of *Lactobacillus* bacteremia—including prior radiotherapy, corticosteroid therapy (defined as a daily dose of >7.5 mg prednisone or the equivalent), or cytotoxic therapy—was recorded. The receipt and duration of antimicrobial treatment during the 0–15 days prior to the bacteremic event was registered. The duration of treatment in the hospital was recorded.

Case definitions. All case patients had ⩾1 blood culture that was positive for *Lactobacillus*. One patient had 2 different episodes of *Lactobacillus* bacteremia 2 years apart, but the isolated strains were not similar, and thus both episodes were included as independent cases. All microorganisms isolated from blood within 1 week were considered to belong to a single case. Bacteremia was defined as polymicrobial if ⩾1 microorganism other than *Lactobacillus* was detected in the same blood culture. Antimicrobial treatment was defined as effective in vitro if the case patient received ⩾1 antimicrobial agent active in vitro against the *Lactobacillus* strain for ⩾7 days. *Lactobacillus* bacteremia was regarded as nosocomial if the case patient had been hospitalized for ⩾48 h before the positive blood culture result.

Statistical analyses. The case patients were divided into 4 groups on the basis of different infecting *Lactobacillus* species, and these groups were compared using analysis of variance (ANOVA) with respect to the continuous variables. However, for survival analyses, all cases associated with *L. rhamnosus* were combined because of the low number of cases. For pairwise comparisons, Fisher's LSD test was used. Logarithmic transformations were carried out for skewed distributions. The χ^2 test or Fisher's exact test was used for nominal variables. Kaplan-Meier survival curves for the duration of survival after the onset of bacteremia and the log-rank test were used to compare the groups. The survival times were described using medians and 95% CIs. In addition, the survival times were analyzed using Cox's regression model, and the group comparisons were analyzed after adjusting for confounding variables. In Cox's regression model, the prognostic variables were entered using the forward stepping procedure. Any P value >.05 was considered statistically significant. Statistical analyses were performed with SPSS computer software (version 10.1).

RESULTS

The 89 *Lactobacillus* bacteremia case patients were divided into 4 groups. Case patients for whom the infecting species of *Lactobacillus* were confirmed were grouped according to species as follows: case patients with *L. rhamnosus* GG isolates (LGG; $n = 11$), case patients with *L. rhamnosus* isolates other than LGG (LR; $n = 14$) and case patients with other confirmed *Lactobacillus* species isolates (OL; $n = 22$). The case patients for whom the infecting species was not confirmed

Table 1. Demographic and clinical characteristics and laboratory values for 89 case patients with *Lactobacillus* bacteremia, by infecting *Lactobacillus* species.

Variable	LGG ($n = 11$)	LR ($n = 14$)	OL ($n = 22$)	NCL ($n = 42$)
Age in years, mean ± SD	60.9 ± 22.6	64.3 ± 18.0	60.1 ± 24.0	53.5 ± 23.3
Men, no. (%) of case patients	5 (45)	8 (57)	11 (50)	27 (64)
Severity classification of underlying disease,[a] no. (%) of case patients				
Classes 1 and 2 (nonfatal)	1 (10)	2 (14)	4 (18)	9 (22)
Class 3 (ultimately fatal)	5 (45)	4 (29)	7 (32)	14 (33)
Class 4 (rapidly fatal)	5 (45)	8 (57)	11 (50)	19 (45)
Temperature >38°C or <36°C, no. (%) of case patients	9 (82)	11 (79)	19 (86)	30 (71)
C-reactive protein level, mean mg/L ±SD				
At the onset of bacteremia	183 ± 117	197 ± 105	92 ± 56[b]	115 ± 99[c]
Maximum[d]	226 ± 104	236 ± 104	118 ± 66[b]	171 ± 107[e]
Leucocyte count, cells × 10^9/L, geometric mean ± SD				
At the onset of bacteremia	4.58 ± 19.75	5.65 ± 8.42	9.12 ± 19.83	5.37 ± 7.62
Maximum	18.55 ± 19.65	14.37 ± 13.79	15.57 ± 3.25	14.18 ± 7.60
Polymicrobial infection, no. (%) of case patients	2 (18)	4 (29)	10 (45)	19 (45)
Duration of hospitalization, mean days ± SD				
Prior to onset of bacteremia, mean	5.1 ± 17.1	7.2 ± 22.7	5.3 ± 22.8	2.7 ± 8.4
After onset of bacteremia	9.2 ± 11.8	11.8 ± 15.9	12.0 ± 9.7	12.5 ± 9.7

NOTE. LGG, case patients with bacteremia caused by *L. rhamnosus* GG; LR, case patients with bactermia caused by *L. rhamnosus* strains other than *L. rhamnosus* GG; NCL, case patients with bacteremia caused by lactobacilli that were not characterized to the species level; OL, case patients with bacteremia caused by specified *Lactobacillus* species other than *L. rhamnosus*.

[a] According to McCabe and Jackson [20] classification.
[b] Compared to all case patients with bacteremia caused by *L. rhamnosus*, $P < .001$.
[c] Compared to all case patients with bacteremia caused by *L. rhamnosus*, $P < .01$.
[d] Within 5 days after the onset of bacteremia.
[e] Compared to all case patients with bacteremia caused by *L. rhamnosus*, $P < .05$.

Table 2. Predisposing factors among 89 case-patients with *Lactobacillus* bacteremia, by infecting *Lactobacillus* species.

Predisposing factor	No. (%) of case patients			
	LGG (n = 11)	LR (n = 14)	OL (n = 21)	NCL (n = 42)
Intravenous catheter	7 (64)	8 (57)	12 (57)	12 (29)
Central venous catheter	6 (55)	5 (36)	8 (38)	14 (33)
Urinary catheter	3 (27)	4 (29)	3 (14)	6 (14)
Intubation	1 (9)	1 (7)	2 (10)	3 (7)
Ventilation support	5 (45)	4 (29)	3 (75)	5 (12)
Previous surgery or endoscopy	5 (45)	9 (64)	14 (67)	15 (36)
Prosthetic material	2 (18)	2 (14)	1 (5)	4 (10)
Neutropenia[a]	3 (27)	2 (14)	1 (5)	9 (21)
Prior antimicrobial therapy	7 (64)	10 (71)	10 (48)	19 (45)
Immuno suppression				
Any	7 (64)	6 (43)	10 (48)	23 (55)
With corticosteroids	2 (18)	4 (29)	6 (29)	12 (29)
With cytotoxic therapy	4 (36)	3 (21)	5 (24)	14 (33)

NOTE. LGG, case patients with bacteremia caused by *L. rhamnosus* GG; LR, casepatients with bactermia caused by *L. rhamnosus* strains other than *L. rhamnosus* GG; NCL, case patients with bacteremia caused by lactobacilli that were not characterized to the species level; OL, case patients with bacteremia caused by specified *Lactobacillus* species other than *L. rhamnosus*.

[a] Neutropenia was defined as $<0.5 \times 10^9$ cells/L.

but with pathogens that had been defined previously as lactobacilli in clinical microbiology laboratories were the fourth group (NCL; $n = 42$).

Demographic characteristics and predisposing factors. Demographic characteristics of the groups were similar, except that case patients in the NCL group were slightly, but not significantly, younger than those in the other groups ($P = .092$; table 1). The majority of case patients in all groups had underlying diseases that were ultimately or rapidly fatal (McCabe classes 3 or 4). These included 91% of case patients in the LGG group, 86% in the LR group, 82% in the OL group, and 79% in the NCL group. The underlying diseases were mainly malignancies or serious gastrointestinal disorders. For example, in the LGG group, 5 case patients had a malignancy—gastrointestinal (2 case patients), hematological (1 case patient), osteal (1 case patient), or mammary (1 case patient)—and 5 case patients had gastrointestinal diseases, such as hepatic cirrhosis (2 case patients), cholecystolithiasis (1 case patient), and chronic pancreatitis (2 case patients). Similarly, in the LR group there were 6 case patients with a malignant disease and 5 case patients with gastrointestinal diseases. The majority of case patients in all groups had undergone a surgical intervention, with no significant differences between the groups (table 2). There were no differences between these 4 groups in the use of foreign devices of any kind (mainly peripheral or central venous catheters and/or urine catheters) or in the proportion of case patients with immunosuppression (table 2).

Antimicrobial therapy was received previously by 52% of case patients, with no significant differences between the groups. β-Lactam antibiotics were used in 94% of cases before the onset of *Lactobacillus* bacteremia, whereas quinolones were used in 20%, metronidazole in 17%, and vancomycin in only 13% of cases.

Laboratory and microbiological findings. Mean blood leukocyte, neutrophil, or thrombocyte counts and the proportions of granulocytopenic case patients did not differ between the groups at the onset of bacteremia or at their peak values within 5 days after the onset of the bacteremic episode (tables 1 and 2). Mean serum glutamine transferase (GOT) and serum creatinine values were not significantly elevated. However, mean serum C-reactive protein levels were significantly higher in the LGG and LR groups than in the OL and NCL groups (table 1).

Polymicrobial bacteremia was found in 39% of case patients, and $\geqslant$2 additional bacteria other than lactobacilli were isolated from 12% of case patients (table 1). Lactobacilli were isolated from deep abscesses in 8 case patients, including 3 case patients in the LR group, 1 case patient in the LGG group, 2 case patients in the OL group, and 2 case patients in the NCL group. Urine samples were obtained from 64% of case patients at the onset of bacteremia, and the urine cultures for 26% of case patients yielded pathogens, but only 1 yielded *Lactobacillus*.

Treatment and clinical outcome. Various antimicrobial agents were used in the treatment. There were no differences between the groups in the average duration of antimicrobial treatment (table 3). Combination therapy with $\geqslant$2 antimicrobial agents was the form of therapy most often used in each group. The distribution of MICs (as determined by Etest) of antimicrobial agents for different *Lactobacillus* species is summarized in table 4. The average number of days of hospitalization prior to or after the onset of bacteremia did not differ significantly between the groups (table 1).

There were no significant differences between the groups with respect to mortality at 1 month ($P = .101$, log-rank test) (table 5). The median duration of survival among case patients with *L. rhamnosus* bacteremia (2.5 months; LR and LGG groups combined) was less by a statistically significant amount than the median duration of survival among patients in the OL group (8.9 months) and the NCL group (34 months) ($P = .0425$, log-rank test). Mortality at 1 month was lower in the LGG group than in the LR group (27% vs. 50%), although it did not reach statistical significance ($P = .343$, log-rank test), and the number of case patients was too small for detailed comparisons. Polymicrobial bacteremia was not associated with a lower rate of survival in any group at 1 month ($P = .864$, log-rank test).

In multivariate analyses, rapidly fatal underlying diseases (McCabe class 4) were a significant predictor of death in case

Table 3. Treatment of 89 case patients with *Lactobacillus* bacteremia, by infecting *Lactobacillus* species.

Variable	Patient group		
	LGG or LR (n = 25)	OL (n = 22)	NCL (n = 42)
Antimicrobial agent(s) administered			
Penicillin	5 (20)	9 (41)	6 (14)
Cephalosporin	12 (48)	12 (54)	31 (74)
Carbapenem	6 (25)	3 (14)	7 (17)
Clindamycin	3 (12.5)	4 (18)	1 (2)
Tetracycline/erythromycin	1 (4)	2 (9)	1 (2)
Fluoroquinolone	10 (40)	5 (23)	2 (5)
Aminoglycoside	5 (21)	1 (4)	7 (17)
Vancomycin	3 (12.5)	3 (14)	6 (14)
No. of antimicrobial agents administered			
1	4 (16)	4 (18)	15 (36)
2	10 (40)	9 (41)	23 (55)
⩾3	10 (40)	8 (36)	4 (9)
None	1 (4)	1 (4.5)	0 (0)
Adequate treatment received[a]	21 (84)	17 (77)	NA
No adequate treatment received[b]	4 (16)	5 (23)	NA
Duration of antibiotic treatment in days, geometric mean ± SD	11.5 ± 18.0	12.1 ± 13.9	16.2 ± 10.1

NOTE. LGG, case patients with bacteremia caused by *L. rhamnosus* GG; LR, case-patients with bactermia caused by *L. rhamnosus* strains other than *L. rhamnosus* GG; NA, not analyzed; NCL, case patients with bacteremia caused by lactobacilli that were not characterized to the species level; OL, case patients with bacteremia caused by specified *Lactobacillus* species other than *L. rhamnosus*.

[a] According to in vitro susceptibility test results, interpreted as described in table 4.

[b] Includes case patients who received inadequte treatment according to the results of in vitro susceptibility tests, case patients for whom the duration of treatment was <7 days, and case patients who received no antimicrobial treatment at all.

patients infected with *Lactobacillus* species (OR, 15.8; $P <$ .001; 95% CI, 4.99–50.2). Infection with *Lactobacillus* isolates that had low MICs (defined as values not exceeding general breakpoints of susceptibility) of the antimicrobial agents used for treatment was associated with significantly lower mortality (OR, 0.22; $P = .020$; 95% CI, 0.063–0.79) if treatment was continued for ⩾7 days. However, antimicrobial treatment for >7 days had no significant effect on mortality (OR, 0.98; $P = .107$; 95% CI, 0.95–1.00). Prior hospitalization (measured in days) had a slight increasing impact on mortality (OR, 1.02; $P = .012$; 95% CI, 1.01–1.04). After adjustment for these predicting variables in multivariate analyses, *L. rhamnosus* bacteremia (i.e., in the LGG and LR groups combined) was associated with a higher mortality rate than was bacteremia caused by *Lactobacillus* species other than *L. rhamnosus* (i.e., in the OL group) (OR, 3.11; $P = .012$; 95% CI, 1.28–7.56).

DISCUSSION

To the best of our knowledge, this study is the largest thus far of patients with *Lactobacillus* bacteremia. It presents clinical data on 89 case patients, with detailed species characterization of blood culture isolates for 53% of these case patients. In our survey, mortality was 26% at 1 month after onset of illness and was 48% at 1 year after onset of illness, whereas a high overall mortality of 69% at 1 year after onset of illness has previously been reported [2]. Cases of *Lactobacillus* bacteremia, as well as associated mortality, were usually associated with severe underlying comorbidities; 82% of all case patients were classified as having either ultimately or rapidly fatal underlying diseases (McCabe classes 3 or 4). Immunosuppression, prior hospitalization, previous antibiotic treatment, and surgery were also common predisposing factors to *Lactobacillus* bacteremia in our study, which is in accordance with the findings of earlier reports [2, 7].

Transient *Lactobacillus* bacteremia following endoscopy has previously been described [22, 23], and 11% of our case patients had undergone endoscopy. Most of the underlying diseases, including cancer, were gastrointestinal (25%) or hepatic (25%), which is in line with experimental data showing that intestinal lactobacilli might be translocated to blood or to the lymphatic system [24, 25]. In contrast to previous studies [10, 26], not a single case of endocarditis associated with *Lactobacillus* bacteremia was found. Other deep infection foci, such as abscesses,

Table 4. Distribution of MICs, as determined by Etest, of antimicrobial agents for the most common *Lactobacillus* species causing bacteremia in 89 patients.

Antimicrobial agent, microorganism	MIC, ug/mL		No. of isolates	
	Observed range	NCCLS BP	With MIC ≤BP[a]	With MIC >BP[a]
Cefuroxime		8		
LGG	2–4		11	0
LR	2–96		9	6
L. fermentum	0.25–12		8	1
L. casei	2–64		6	1
Imipenem		4		
LGG	0.5–2.0		11	0
LR	0.25–4		15	0
L. fermentum	0.012–0.32		9	0
L. casei	0.38–2		7	0
Vancomycin		4		
LGG	>256		0	11
LR	>256		0	15
L. fermentum	>256		0	9
L.casei	>256		0	7
Ciprofloxacin		1		
LGG	0.25–0.50		11	0
LR	0.25–0.50		15	0
L. fermentum	3–32		0	9
L. casei	0.5–1		7	0
Benzylpenicillin		0.12		
LGG	0.25–1.0		0	11
LR	0.19–0.75		0	15
L. fermentum	0.13–0.38		0	9
L. casei	0.25–2.0		0	7
Netilmicin		8		
LGG	1.5–4		11	0
LR	1.5–4		15	0
L. fermentum	0.032–0.19		9	0
L. casei	1–3		7	0

NOTE. The number of isolates tested, by microorganism, was as follows: *L. rhamnosus* GG (LGG), 11 isolates; *L. rhamnosus* strains other than *L. rhamnosus* GG (LR), 15 isolates; *L. fermentum*, 9 isolates; *L. casei*, 7 isolates. BP, breakpoint.

[a] Relative to the breakpoints recommended by the NCCLS for bacterial isolates grown aerobically [19].

were also found in only a few case patients [26]. The majority of *Lactobacillus* bacteremia cases occurred within 48 h after hospitalization, whereas most cases have previously been reported to be nosocomial [2]. However, the majority of the polymicrobial cases in our study were nosocomial. In our study, only 39% of the cases were polymicrobial, in contrast to previous reports in which the proportions of polymicrobial cases were 60% [2] and 87% [3]. The high proportion of community-acquired cases of *Lactobacillus* bacteremia was not due to increased probiotic use of *L. rhamnosus* GG at the time the data was collected, as the incidence of *Lactobacillus* bacteremia remained constant [11].

Prior therapy with antibiotics ineffective against *Lactobacillus* has previously been regarded as a risk factor for a bacteremic episode [2], but one-half of our case patients were receiving ongoing antibiotic treatment at the onset of bacteremia, representing so-called "breakthrough" bacteremic cases. Combination therapy with penicillin and an aminoglycoside has usually been recommended for treatment of bacteremic *Lactobacillus* infections [9, 27]. In our survey, broad-spectrum cephalosporins and carbapenems were used as part of combination therapy to treat >50% of case patients, whereas only 13 case patients received aminoglycosides. However, this study cannot give answers as to which specific antibiotics should be

Table 5. Cumulative survival of 89 case patients with *Lactobacillus* bacteremia according to Kaplan-Meier analyses.

Case patient group	No. of case patients	No. (%) of case patients surviving[a]		
		After 7 days	After 30 days	After 1 year
LGG	11	8 (73)	8 (73)	6 (55)
LR	14	11 (79)	7 (50)	4 (29)
OL[b]				
All organisms	22	19 (86)	17 (77)	13 (59)
L. fermentum	9	8 (89)	6 (67)	2 (22)
L. casei	7	5 (71)	5 (71)	3 (43)
NCL	42	40 (95)	34 (81)	25 (60)
All	89	78 (88)	66 (74)	46 (52)

NOTE. LGG, case patients with bacteremia caused by *L. rhamnosus* GG; LR, case patients with bactermia caused by *L. rhamnosus* strains other than *L. rhamnosus* GG; NCL, case patients with bacteremia caused by lactobacilli that were not characterized to the species level; OL, case patients with bacteremia caused by specified *Lactobacillus* species other than *L. rhamnosus*.

[a] Duration of survival is measured from onset of bacteremia.

[b] Data for case patients in the OL group with bacteremia caused by *L. jensenii* (2 case patients), *L. gasserii* (2), *L. sake* (1), and *L. zeae* (1) are not shown separately.

used in the treatment of *Lactobacillus* bacteremia, because the clinical data was collected retrospectively.

In previous reports, *Lactobacillus* isolates have been analyzed to the species level in only a few cases [2, 7, 26], and therefore cases with blood culture isolates that were characterized to the species level were included in our study to enhance its epidemiological coverage and comparability. *L. rhamnosus* was the most common species, and it constituted 53% of the isolates. It was also associated with polymicrobial cases, though less frequently. The proportions of *L. fermentum* (20% of isolates) and *L. casei* (15% of isolates) were smaller than previously reported [2, 10, 26]. Furthermore, patients with bacteremia caused by*L. fermentum* and *L. casei* seemed to have clinical features similar to those of patients with *L. rhamnosus* bacteremia. The amount of data is, however, too small for detailed comparisons of various *Lactobacillus* species. It also has to be emphasized that the clinical data has been collected retrospectively and thus can contain only data recorded in medical records. Furthermore, in 47% of cases, no detailed species characterization could be made, and the results from these cases are presented separately. Of these latter cases, about one third would, on further analyses, be shown to result from other bacteria than lactobacilli, as previously shown [11]. Furthermore, the contribution of other concomitant bacteria to the results cannot be totally ruled out, as 39% of the cases were polymicrobial, although polymicrobial bacteremia was not found to be associated with higher mortality.

In most case patients, *Lactobacillus* bacteremia was associated with clear signs of clinical illness, including fever, elevated leukocyte counts, and elevated C-reactive protein values. Measured by elevated C-reactive protein levels, *L. rhamnosus* caused more-severe infections or higher proinflammatory responses, compared with other species. However, serious septicemic complications were detected in only a few cases in the entire study. Four case patients developed multiorgan failure, 6 needed mechanical ventilation, and 11 required vasoactive agents to elevate blood pressure. Therapy that was appropriate according to in vitro susceptibility testing results significantly reduced the risk of death in multivariate analysis (OR, 0.22; $P < .05$), compared with therapy that was ineffective according to in vitro results. The results of this study indicate that the detection of lactobacilli in blood culture is of clinical significance and that the antimicrobial susceptibility of the lactobacilli should guide treatment decisions.

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