MAJOR ARTICLE

Saccharomyces cerevisiae Fungemia: An Emerging Infectious Disease

Patricia Muñoz,[1] Emilio Bouza,[1] Manuel Cuenca-Estrella,[3] Jose María Eiros,[1] Maria Jesús Pérez,[2] Mar Sánchez-Somolinos,[1] Cristina Rincón,[2] Javier Hortal,[2] and Teresa Peláez[1]

Departments of [1]Clinical Microbiology and Infectious Diseases and [2]Heart Surgery, Hospital General Universitario "Gregorio Marañón," Universidad Complutense, and [3]Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain

(See the editorial commentary by Herbrecht and Nivoix on pages 1635–7)

Background. *Saccharomyces cerevisiae* is well known in the baking and brewing industry and is also used as a probiotic in humans. However, it is a very uncommon cause of infection in humans.

Methods. During the period of 15–30 April 2003, we found 3 patients with *S. cerevisiae* fungemia in an intensive care unit (ICU). An epidemiological study was performed, and the medical records for all patients who were in the unit during the second half of April were assessed.

Results. The only identified risk factor for *S. cerevisiae* infection was treatment with a probiotic containing *Saccharomyces boulardii* (Ultralevura; Bristol-Myers Squibb). This probiotic is used in Europe for the treatment and prevention of *Clostridium difficile*–associated diarrhea. The 3 patients received the product via nasograstric tube for a mean duration of 8.5 days before the culture result was positive, whereas only 2 of 41 control subjects had received it. Surveillance cultures for the control patients admitted at the same time did not reveal any carriers of the yeast. Strains from the probiotic capsules and the clinical isolates were identified as *S. cerevisiae*, with identical DNA fingerprinting. Discontinuation of use of the product in the unit stopped the outbreak of infection. A review of the literature identified another 57 cases of *S. cerevisiae* fungemia. Overall, 60% of these patients were in the ICU, and 71% were receiving enteral or parenteral nutrition. Use of probiotics was detected in 26 patients, and 17 patients died.

Conclusions. Use of *S. cerevisiae* probiotics should be carefully reassessed, particularly in immunosuppressed or critically ill patients.

Saccharomyces cerevisiae is a well-known yeast used in the food industry. It has now been demonstrated that this yeast can cause different forms of invasive infection [1–3], frequently after administration as a probiotic for the treatment of antibiotic-related diarrhea [4]. We report an outbreak of *S. cerevisiae* fungemia in an intensive care unit (ICU) that was traced, by means of molecular methods, to the use of probiotics, and we review all cases of *S. cerevisiae* fungemia that have been reported in the literature.

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Reprints or correspondence: Dr. Patricia Muñoz, Hospital General Universitario "Gregorio Marañón," Doctor Esquerdo 46, 28007 Madrid, Spain (pmunoz@micro.hggm.es).

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PATIENTS, MATERIALS, AND METHODS

Setting. Our hospital is a 1750-bed, tertiary care, referral, general teaching institution. The heart surgery ICU of our hospital is a 14-bed postsurgery unit for all adult patients who have undergone a major cardiac surgical procedure.

Study of the outbreak of infection. During the period of 15–30 April 2003, we detected 3 patients with *S. cerevisiae* fungemia in our ICU. The medical records for 41 patients who had been in the unit during the second half of April 2003 were reviewed, in accordance with an established protocol, for epidemiological data, presence of *Clostridium difficile*–associated diarrhea, and use of *Saccharomyces boulardii* probiotic. Feces and pharynx surveillance cultures for the 14 patients in the ICU were also performed when the outbreak of infection was detected to test for *S. cerevisiae* carriage. Capsules of the probiotic were obtained for culture.

Table 1. Characteristics of 60 patients with fungemia caused by *Saccharomyces cerevisiae.*

Patient	Age in years, sex	Underlying condition or risk factor	Parenteral or enteral nutrition received	IV catheter	ICU stay	Sb probiotic use	Time to fungemia, days	Previous antimicrobial therapy	Other positive culture results	Disease	Therapy	Outcome	Reference(s)
1	54, F	Prosthetic valve endocarditis	NR	Yes	Yes	No	NA	Yes	Urine	Possible PVE	AmB	Survived	[10]
2	38, M	IDA, prosthetic tricuspid valve	NR	Yes	No	No	NA	Yes	No	Fungemia	AmB, surgery	Survived	[11, 12]
3	68, M	Ingestion of viable organism	No	No	No	No	NA	No	Urine, bone marrow	Disseminated	None	Survived	[13]
4	59, M	Burn	P	Yes	Yes	No	NA	Yes	Esophageal biopsy	Esophageal ulcer	AmB	Survived	[14]
5	61, M	RF, acute abdomen	NR	Yes	Yes	No	NA	Yes	CVC access site	Fungemia	Mico, 5FC	Died	[15]
6	37, F	HIV infection, RF, peritoneal dialysis	NR	Yes	NR	NR	NA	Yes	No	Fungemia	AmB	Survived	[18]
7	26, M	Nonneutropenic AML	NR	Yes	NR	NR	NR	No	No	Fungemia	NR	Survived	[17]
8	25, F	Multiple trauma	NR	Yes	Yes	No	NA	Yes	No	Fungemia	AmB	Survived	[18]
9	81, F	AML	NR	Yes	NR	NR	NR	NR	NR	Fungemia	AmB	Survived	[17]
10	62, F	Pancreatic cancer, hepatic abscesses	NR	Yes	NR	No	NA	Yes	Biliary fluid, liver abscess	Liver abscess	AmB	Died	[19]
11	65, F	Idiopathic pancytopenia, pneumonia, splenectomy, tuberculosis	NR	Yes	NR	No	NA	Yes	Lung biopsy, colon, heart, pericardium	Disseminated	None	Died	[19]
12	71, M	Aplastic anemia, neutropenia	NR	Yes	NR	No	NA	Yes	Throat	Fungemia	AmB, 5FC	Died (NRe)	[20]
13	0.1, NR	Abdominal surgery, respiratory failure	P	Yes	NR	No	NA	Yes	Urine	Fungemia	CVC removal	Survived	[20]
14	33, M	Ulcerative colitis, corticosteroid therapy, colectomy, RF	P/E	Yes	Yes	Yes	5	Yes	No	Fungemia	Flu, AmB	Survived	[21]
15	30, F	Allogeneic BMT	NR	Yes	NR	NR	NR	NR	No	Fungemia	NR	Cured	[22]
16	70, M	Myelodysplastic syndrome, tuberculosis	No	Yes	No	No	NA	Yes	No	Fungemia	None	Died	[23]
17	1, F	Bronchopneumonia	P	Yes	NR	Yes	13	Yes	No	Fungemia	Flu	Survived	[24]
18	14, M	Burn	E	Yes	Yes	Yes	102	Yes	No	Fungemia	5FC, AmB	Survived	[25]
19	NR	Prosthetic valve	NR	Yes	NR	NR	NA	Yes	NR	PVE	Surgery, AmB	Survived	[26]
20	48, F	BMT due to CML, GVHD	NR	Yes	No	No	NA	Yes	…	Fungemia	Flu	Survived	[27]
21	32, F	Self-inflicted fungemia; breast abscess	No	No	No	No	NA	No	No	Fungemia	…	Survived	[28]
22	16, M	Self-inflicted fungemia; convulsion	No	No	No	No	NA	No	No	Fungemia	…	Survived	[28]
23	34, M	Relapsed ALL	NR	Yes	No	No	NA	Yes: Flu	No	Fungemia	AmB	Died	[29]
24	49, M	Aspiration pneumonia	E	Yes	No	Yes	8	Yes	No	Fungemia	Flu	Survived	[30]
25	51, F	Polyarteritis nodosa (corticosteroids and cyclophosphamide therapy), CDAD	No	Yes	NR	Yes	18	Yes	No	Fungemia	AmB	Survived	[31]
26	10, F	Cystic fibrosis, bowel obstruction, biliar cirrhosis	P	Yes	No	Vicinity	NA	Yes	Postmortem lung, blood, mitral thrombus	Disseminated	AmB	Died	[32]
27	<1, M[a]	Congenital malformation	P	Yes	Yes	Vicinity	NA	Yes	No	Fungemia	AmB	Survived	[32]
28	7, M	Partial intestinal resection, parenteral nutrition	P	Yes		Vicinity	NA	Yes	No	Fungemia	AmB	Survived	[32]
29	85, M	Multiple trauma	NR	Yes	NR	NR	NA	Yes	No	Fungemia	AmB	Survived	[33]

30	78, M	COPD, diarrhea	E	Yes	Yes	Yes	21	Yes	No	Fungemia	Flu	Survived	[34]
31	<1, M[b]	Acute myeloid leukemia, neutropenia	No	Yes	No	Yes	NR	Yes: Flu	No	Fungemia	AmB	Survived	[35]
32	<1, M[c]	Congenital cardiopathy, diarrhea	P	Yes	Yes	Yes	10	Yes	No	Fungemia	L-AmB	Survived	[36]
33	<1, F[c]	Intestinal atresia	P	Yes	Yes	Vinity	NA	NR	No	Fungemia	AmB	Survived	[36]
34	74, M	Neurosurgery	E	No	Yes	Yes	NR	NR	No	Fungemia	Flu	Died	[37]
35	57, F	Prosthetic valve, endocarditis	No	No	No	No	NA	Yes	Aortic root abscess	PVE	Keto, partial surgical excision	Died	[38, 39]
36	2, M	Small bowel resection, cystic fibrosis	E	Yes	No	Yes	300	Yes	No	Fungemia	AmB	Survived	[40]
37	36, M	AIDS, lymphoma, MAID	P	Yes	No	Yes	7	Yes	No	Fungemia	Flu	Survived	[40]
38	47, M	Esophagectomy, pneumonia	P/E	Yes	No	Yes	10	Yes	Catheter	Fungemia	Flu	Survived	[40]
39	78, F	ARDS, peptic ulcer, RF	E	Yes	Yes	Yes	53	Yes	No	Fungemia	None	Survived	[40]
40	59, F	Cirrhosis, DM, peritonitis	P	Yes	Yes	No	NA	Yes	Vagina, RT, liver abscess	Disseminated	Flu, AmB	Died	[41]
41	<1, F[a]	Newborn	E	Yes	Yes	No	NA	Yes	No	Fungemia	AmB	Survived	[42]
42	<1, M[a]	Premature birth, ductus arteriosus, necrotizing enterocolitis	NR	Yes	Yes	No	NA	Yes	No	Endocarditis	AmB, Flu	Survived	[43]
43	56, M	Aortic-femoral graft, aortoenteric fistula	NR	Yes	No	No	NA	Yes	Periaortic fluid	Aortic graft infection	AmB	Died	[44]
44	50, M	Cardiac arrest	E	Yes	Yes	Yes	10	NR	…	Fungemia	None	Died (NRe)	[45]
45	51, F	Aortic surgery, cachexia	E	Yes	Yes	Yes	9	NR	…	Fungemia	Flu	Died (NRe)	[45]
46	50, M	ARDS, gastric ulcus	E	Yes	Yes	No	1	NR	Catheter	Fungemia	Flu	Survived	[45]
47	82, F	Acute respiratory failure	E	Yes	Yes	Yes	12	NR	No	Fungemia	None	Survived	[45]
48	75, M	Acute respiratory failure	E	Yes	Yes	Yes	14	NR	No	Fungemia	None	Survived	[45]
49	77, M	Peritonitis, duodenal ulcus	E	Yes	Yes	Yes	4	NR	No	Fungemia	AmB	Died (NRe)	[45]
50	71, F	Cerebrovascular stroke	E	Yes	Yes	Yes	9	NR	No	Fungemia	None	Survived	[45]
51	34, M	Head trauma	E	Yes	Yes	Vicinity	NA	Yes	No	Fungemia	Flu	Survived	[3]
52	48, M	Cerebral aneurism	E	Yes	Yes	Vicinity	NA	Yes	No	Fungemia	Flu	Survived	[3]
53	75, F	Myocardial infarction	E	Yes	Yes	Vicinity	NA	Yes	Catheter	Fungemia	Flu	Survived	[3]
54	35, F	Multiple trauma	E	NR	NR	NR	NA	NR	NR	Fungemia	NR	Survived	[3]
55	42, F	Kidney/pancreas transplant	No	Yes	No	Yes	7	Yes	No	Fungemia	Flu	Survived	[46]
56	41, M	DM, RF, HIV infection, tuberculosis, syphilis	No	Yes	No	Yes	15	Yes	No	Fungemia	AmB	Survived	[46]
57	<1, M[a]	Parenteral nutrition	P	Yes	Yes	Yes	4	No	No	Fungemia, methemoglobinemia	L-AmB	Survived	[47]
58	76, F	DM, heart surgery	P/E	Yes	Yes	Yes	9	Yes	Catheter	PVE	Flu	Died	PR
59	72, F	Heart surgery	P/E	Yes	Yes	Yes	7	Yes	Catheter hub	Fungemia	None	Died	PR
60	74, F	Rheumatoid arthritis, heart surgery	P/E	Yes	Yes	Yes	8	Yes	No	Fungemia	Flu	Died	PR

NOTE. ALL, acute lymphocytic leukemia; AmB, amphotericin B; AML, acute myelogenous leukemia; ARDS, acute respiratory distress syndrome; BMT, bone marrow transplantation; CDAD, *Clostridium difficile*–associated diarrhea; CML, chronic myelogenous leukemia; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; DM, diabetes mellitus; E, enteral; 5FC, 5-fluorocytosine; Flu, fluconazole; GVHD, graft-versus-host disease; IDA, injection drug abuser; Keto, keotconazole; L-AmB, liposomal amphotericin B; MAID, *Mycobacterium avium* intracellulare disease; Mico, miconazole; NA, not applicable; NR, not reported; NRe, nonrelated; P, parenteral; PR, present report; PVE, prosthetic valve endocarditis; RF, renal failure; Sb, *Saccharomyces boulardii*.

[a] Seven months old.
[b] Eight months old.
[c] One month old.

Identification of fungal isolates and susceptibility testing. One isolate from each patient with *S. cerevisiae* fungemia and the strain recovered from the probiotic capsules (the 4 study strains) were sent to the Mycology Reference Laboratory of the National Center for Microbiology of Spain (Madrid) for definitive identification and susceptibility testing. The isolates were identified by routine morphological and physiological tests [5, 6].

Susceptibility testing was conducted strictly on the basis of recommendations proposed by the Antifungal Susceptibility Testing Subcommittee of the European Committee on Antibiotic Susceptibility Testing for testing of fermentative yeasts (AFST-EUCAST discussion document 7.1) [7]. *Candida parapsilosis* ATCC22019 and *Candida krusei* ATCC6258 were used as quality-control strains.

The antifungal agents used in the study were amphotericin B, flucytosine, fluconazole, itraconazole, and voriconazole. These agents were dissolved in 100% dimethylsulfoxide (Sigma Aldrich Quimica). The MICs were determined at 24 and 48 h. MICs were obtained by measuring the absorbance at 530 nm with an MRXII reader (Dynatech; Cultek). For amphotericin B, the MIC end points were defined as the lowest drug concentration exhibiting reduction in growth of $\geqslant$90%, compared with that of the control growth. For flucytosine and azole drugs, the MIC end point was defined as the lowest drug concentration exhibiting a reduction in growth of 50%.

Molecular typing studies. Typing studies were performed on the basis of previously described procedures [8, 9]. The PCR fingerprinting procedure, which included 3 different primers, was used for molecular typing. The phage M13 core sequence (5′-GAGGGTGGCGGTTCT-3′) and primers that targeted microsatellite sequences $(GTG)_5$ and $(GACA)_4$ were used to amplify the DNA of the different strains. Amplification reactions were done in accordance with methods described in the literature [8, 9]. Amplifications were performed in a thermal cycler (GenAmp PCR System 2700; Applied Biosystems). Each amplification was repeated at least twice to verify the presence or absence of the scored bands. The amplified products were electrophoresed through 1.3% agarose gels (Pronadisa) and were stained with ethidium bromide (Sigma Aldrich Química). After intensive washing with distilled water, gels were photographed under UV light. PCR profiles were analyzed visually and indexed by letters or numbers, and even a single mismatch led to a different letter or number code.

Eight other clinical isolates of *S. cerevisiae* were used as control organisms in molecular typing studies (i.e., control strains). All strains were recovered over a 7-year period (1997–2003) from 8 different Spanish hospitals. Each clinical isolate represented a single isolate from a patient. These control isolates were not geographically or temporally related.

Statistical analysis. Relationships between variables were evaluated using the χ^2 statistic for categorical variables, Student's *t* test for normally distributed continuous variables, and the Mann-Whitney *U* test for nonparametric comparisons. All comparisons were considered to be statistically significant if the *P* value was $\leqslant$.05. Statistical analysis was performed using the SPSS software system (SPSS).

RESULTS

Case Reports

During the period of 15–30 April 2003, a total of 3 patients admitted to the major heart surgery ICU at our institution were found to have blood cultures positive for *S. cerevisiae*. These cases are described briefly below and in table 1.

Patient 1. Patient 1 was a 72-year-old woman who had undergone heart surgery on 14 March 2003. She had a complicated postoperative period, with multiple bacterial infections and *C. difficile*–associated diarrhea, for which she received Ultralevura (Bristol-Myers Squibb) starting on 8 April. On 15 April, she developed *S. cerevisiae* fungemia. Further culture results were negative, and no antifungal therapy was provided. The patient unexpectedly died on 29 April.

Patient 2. Patient 2 was a 74-year-old woman with rheumatoid arthritis who was receiving corticosteroid therapy. She required emergency replacement of her prosthetic mitral valve, and after her operation, she experienced different nosocomial infections, which required treatment with broad-spectrum antimicrobials, and *C. difficile*–associated diarrhea, for which Ultralevura was prescribed starting on 16 April.

On 23 April 2003, the patient developed sepsis and *S. cerevisiae* fungemia. The patient was treated with fluconazole (400 mg q.d.). The results of tip catheter and urine cultures were negative. She died on 5 May of catheter-related *Enterococcus faecium* bacteremia.

Patient 3. Patient 3 was a 76-year-old woman who required a mitral valve replacement and 4-vessel coronary artery bypass grafting on 4 April 2003. Her postoperative course was complicated by a perioperative myocardial infarction. She experienced diverse nosocomial infections and *C. difficile*–associated diarrhea, and she started receiving Ultralevura on 22 April. On 30 April, she developed sepsis and persistent *S. cerevisiae* fungemia. The probiotic treatment was stopped, and fluconazole (400 mg q.d.) was administered. A transesophageal echocardiogram revealed a vegetation on the prosthetic valve. The patient died on 20 June after a CNS stroke.

Colonization Surveillance

The results of feces and pharynx surveillance cultures for the 14 patients admitted to the unit when the outbreak of infection was recognized were negative for *S. cerevisiae*. No case of asymptomatic carriage was detected.

Role of Ultralevura Probiotic

The 3 case patients were treated with a probiotic preparation before the fungemia (Ultralevura), whereas only 2 of 41 control patients admitted to the ICU during April 2003 had received it. Capsules of the probiotic Ultralevura contain lyophilized *S. boulardii* and were opened and dissolved in the ICU before nasogastric administration. No further cases have been detected since the use of Ultralevura was discontinued in the unit.

The culture of the probiotic capsules showed heavy growth of a yeast (>1,000,000 cfu/mL) similar to that recovered from the 3 fungemic patients. All of the yeasts were identified as *S. cerevisiae.*

Results of Susceptibility and Molecular Typing Tests

The susceptibility results for the 4 *S. cerevisiae* study strains (1 from each patient and 1 from the probiotic batch) are shown in table 2. The molecular typing findings are shown in table 3. This table displays the genomic profile of the 4 study strains and of the other 8 *S. cerevisiae* isolates that acted as control organisms. Patterns obtained with primer M13 are shown in figure 1*A*, and profiles obtained with $(GACA)_4$ are shown in figure 1*B*. The most discriminative primer was the M13 sequence. This primer yielded 7 different patterns of bands for control organisms. Five patterns (A–E) were observed when $(GACA)_4$ was used, and 4 profiles *(a–d)* were observed with the $(GTG)_5$ sequence. When the results obtained with the 3 primers were combined, the 8 control isolates were differentiated, and each control strain was classified into a different genomic type. The profiles were reproducible between different DNA preparations from the same strain, as well as between runs when samples were run a second time.

With regard to the 4 study strains that were isolated from the probiotic and from the 3 temporally related patients, the genomic patterns were identical regardless of the typing technique utilized. This could indicate that the 4 isolates were epidemiologically related.

Review of the Literature about All Cases of S. cerevisiae Fungemia

We searched the MEDLINE database for articles in English, French, or Spanish that were published since 1966 using the medical subject headings "cerevisiae" "boulardii," and "fungemia." We searched reference lists to identify additional reports of *S. cerevisiae* fungemia. Cases with insufficient clinical information were excluded from this analysis [48–51]. Patients in whom the microorganism was not isolated from blood were also excluded [19, 52–56].

We were able to identify 60 cases of *S. cerevisiae* fungemia, including the 3 reported by our group in this article. The most important characteristics of these patients are presented in table 1.

The mean age ($\pm$SD) of the patients was 43 $\pm$ 26.8 years, and 7 patients were $\leqslant$1 year of age. Sex was reported for 57 patients, 31 (54.4%) of whom were male. Only 3 patients were healthy before the fungemia (2 patients with self-inflicted fungemia, who had infected themselves to escape from a prison camp, and 1 patient who ingested large quantities of brewer's yeast as a nutritional supplement). Overall, 28 (60%) of 47 patients whose data were reported were in the ICU when the fungemia was diagnosed, 35 (71%) of 49 were receiving enteral or parenteral nutrition, 55 (93%) of 59 had a central venous catheter in place, and 44 (88%) of 50 had received broad-spectrum antimicrobials. Results of catheter-tip cultures were positive for 6 patients (10%).

The use of probiotics was reported for 26 (45.6%) of 57 patients, and 5 other patients (9%) with fungemia were in the vicinity of patients receiving this therapy. The fungemia was detected a median ($\pm$SD) of 10 $\pm$ 62.3 days (range, 4–300 days) after the administration of the probiotic. Typing procedures were used in 39% of cases, and the capsules were cultured in 13%.

We compared patients who had and who had not received previous Ultralevura probiotic therapy. The only significant differences between the 2 groups were that patients who received probiotic therapy were more commonly in the ICU (70% vs 41%; $P = .05$), were more likely to have received parenteral or enteral nutrition (84% vs 50%; $P < .01$), and were less frequently treated with amphotericin B (32% vs 65%; $P = .01$).

The clinical presentation consisted of isolated fungemia (49 [82%] of 60 patients), endocarditis or periaortic abscess (5 [8.3%] of 60), disseminated disease (4 [6.7%] of 60), liver abscess (1 [1.7%] of 60), and esophageal ulcer (1 [1.7%] of

Table 2. Susceptibility test results for 4 epidemiologically related *Saccharomyces cerevisiae* strains isolated at a tertiary care hospital.

	MIC, μg/mL				
Strain ID	Amphotericin B	Flucytosine	Fluconazole	Itraconazole	Voriconazole
CNM-CL-5091	0.50	0.25	8.0	2.0	0.12
CNM-CL-5092	0.50	0.12	8.0	1.0	0.12
CNM-CL-5093	0.50	0.12	8.0	1.0	0.25
CNM-CL-5094	0.50	0.12	8.0	2.0	0.12

NOTE. CNM-CL, yeast collection of Spanish National Center for Microbiology.

Table 3. Molecular typing patterns for 4 epidemiologically related *Saccharomyces cerevisiae* strains isolated at a tertiary care hospital (study strains) and for 8 control strains.

Strain	Isolation site	Molecular typing pattern			Typing code	Genomic type
		M13	$(GACA)_4$	$(GTG)_5$		
Control strains						
CNM-CL-2780	Oropharyngeal exudate	1	A	*a*	1A*a*	I
CNM.CL-3831	Skin biopsy specimen	2	A	*b*	2A*b*	II
CNM-CL-4080	Bronchial secretion	3	B	*b*	3B*b*	III
CNM-CL-4238	Bronchial secretion	4	A	*b*	4A*b*	IV
CNM-CL-4256	Pleural fluid	1	B	*b*	1B*b*	V
CNM-CL-4456	Vaginal exudate	5	C	*a*	5C*a*	VI
CNM-CL-4542	Oropharyngeal exudate	6	D	*c*	6D*c*	VII
CNM-CL-4670	Blood	7	E	*d*	7E*e*	VIII
Study strains						
CNM-CL-5091	Ultralevura[a]	1	B	*b*	1B*b*	V
CNM-CL-5092	Blood	1	B	*b*	1B*b*	V
CNM-CL-5093	Blood	1	B	*b*	1B*b*	V
CNM-CL-5094	Blood	1	B	*b*	1B*b*	V

NOTE. Genomic profiles are indexed by letters or numbers.

[a] Manufactured by Bristol-Myers Squibb.

60). All but 12 patients received antifungal therapy (20%). The most common drugs received were fluconazole (16 patients) and amphotericin B (28 patients). The mortality rate was 28% (17 of 60 patients died). The only factor that increased the mortality rate was older age (mean age of patients who died and who survived, 60 years and 36 years, respectively; $P < .001$)

DISCUSSION

The extent of this review indicates that *S. cerevisiae* should be considered as a well-established cause of nosocomially acquired yeast infection, particularly in patients receiving prophylaxis or treatment with the probiotic Ultralevura *(S. boulardii),* which should be considered a risk factor for nosocomial bloodstream infection in patients with predisposing underlying conditions.

Saccharomyces is a ubiquitous ascomycetous yeast used by the food industry in the production of foodstuffs, wines, and beers. The identification of *S. cerevisiae* in the laboratory is not problematic and is usually based on the morphology of the yeast, its growth pattern, and biochemical studies (figure 1) [10].

The genus *Saccharomyces* includes several species, the most well-known being *S. cerevisiae.* Genotyping techniques, such as rDNA sequencing and random amplified polymorphic DNA analysis, have been used to identify isolates of *Saccharomyces* to the species level [36, 44, 48, 57]. After some discussion [58], *S. boulardii,* which is approved in many countries for the treatment or prevention of antibiotic-associated diarrhea, is now considered to be identical to a particular strain of *S. cerevisiae* [1, 46, 57]. This evidence is also supported by clinical studies such as ours, in which *S. cerevisiae* recovered from patients and *S. boulardii* strains isolated from probiotic preparations were proved to be genomically identical [3, 25, 30, 31, 36, 40, 45, 46].

The incidence of *S. cerevisiae* fungemia is unknown, although population-based studies suggest that it is responsible for 0.1%–3.6% of all episodes of fungemia [45, 48, 49]. The first case was reported in 1970 in a patient with a prosthetic mitral valve [10], and analysis of our review reveals an increase in the number of cases reported during the past decade (there were 4 cases reported during 1970–1980, 10 reported during 1981–1991, and 46 reported during 1992–2004).

S. cerevisiae is a common colonizer of mucosal surfaces and part of the normal flora of the gastrointestinal tract, the respiratory tract, and the vagina [59]. Its presence in normally sterile fluids has been classically described in patients with rupture of the local barriers or with very high fungal loads. Portals of entry include translocation of ingested microorganisms from the enteral or oral mucosa [24, 25, 37, 41, 51] and contamination of intravenous catheter insertion sites [40]. In our review, catheter tip culture results were positive in 6 cases (9.8%).

Hospital-acquired transmission has been demonstrated [3, 36, 45, 59], and both transmission from the environment and person-to-person transmission are possible [45, 52, 60]. *S. cerevisiae* fungemia may also be a self-inflicted disease [13, 28]. Finally, the difference in virulence between clinical and nonclinical strains may explain different degrees of invasiveness [1, 61, 62]

The most consistent risk factor for *S. cerevisiae* fungemia is the use of probiotics. Despite the fact that, in many cases, the

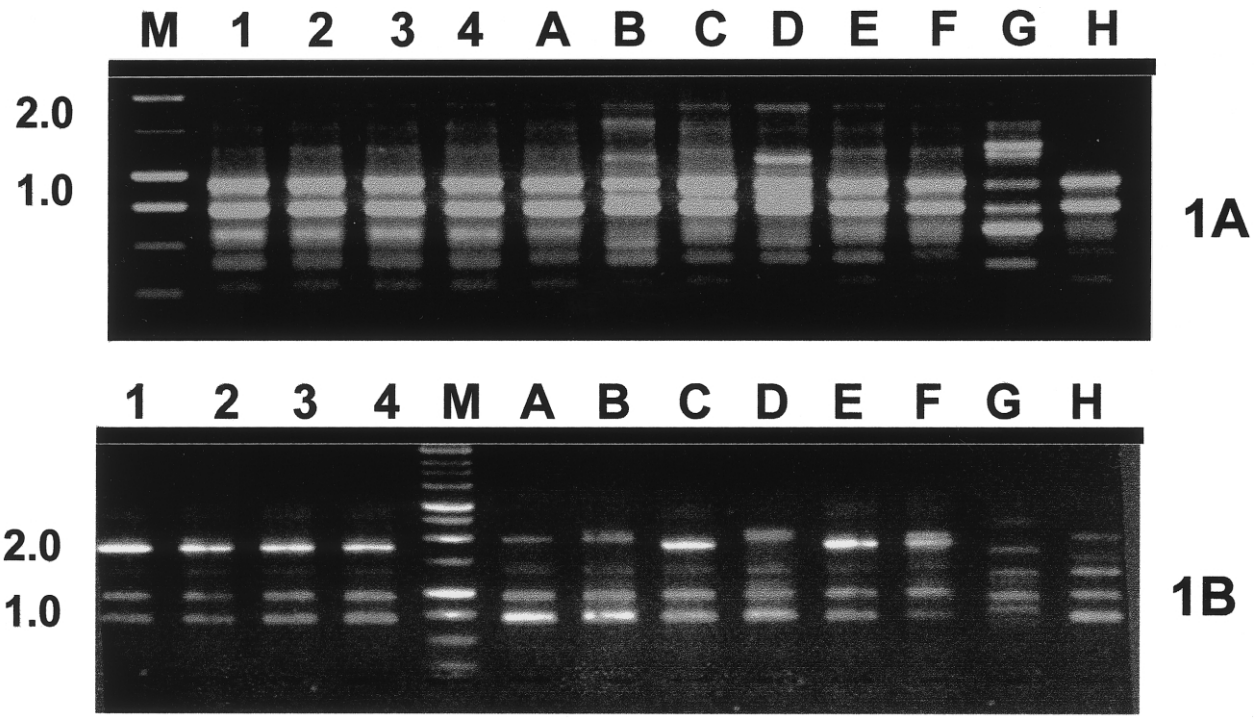

Figure. 1. PCR fingerprinting profiles obtained with primer M13 *(A)* and primer $(GACA)_4$ *(B). Lane M,* molecular marker (sizes in Kb), 1-kb ladder (Pharmacia; Madrid, Spain); *lanes A–H,* control strains (according to table 3); *lanes 1–4,* study isolates recovered from patients who were temporally related (according to table 3).

use of Ultralevura was not specified, 26 cases of *S. cerevisiae* fungemia—including ours—have been directly related to the oral administration of Ultralevura [15, 16, 18, 24, 25, 27, 30, 31, 34–37, 40, 45, 46]. In another 5 cases, the fungemic patients were reported to have been in the vicinity of probiotic-treated patients [3, 36, 45]. Fungemia was detected a median of 10 days after the administration of the probiotic (range, 4–300 days).

The use of probiotics may be especially dangerous in patients at high risk for infection. In fact, 15 of the 26 patients who developed fungemia after receipt of probiotic therapy were reported to be in the ICU, were receiving enteral feeding, had a central venous catheter in place, and were receiving antimicrobials. In these ICUs, at least 2 outbreaks (besides ours) have been described [3, 45]. It has been demonstrated that, when the probiotic capsules are opened for administration through the nasogastric tube, viable yeasts may be detected at a 1-m distance as a result of aerial transmission, and the yeasts persist on room surfaces after 2 h. They can be detected on the bare hands of health care workers even after vigorous hand washing [40]. In this setting, central venous catheters may be easily contaminated and become the portal of entry [40]. *S. cerevisiae* was recovered from the catheter hub of 1 of our patients, and catheter-related fungemia was further demonstrated by means of lysis centrifugation blood cultures.

As previously mentioned, classic severe immunosuppression is not a prerequisite for developing *S. cerevisiae* fungemia. In our review, 35 (71%) of the 49 patients with fungemia were receiving enteral or parenteral nutrition, 55 (93%) of 59 had a central venous catheter in place, and 44 (88%) of 50 had received broad-spectrum antimicrobials.

S. cerevisiae can cause a wide variety of clinical syndromes, such as pneumonia [19, 54], empyema [56], liver abscess [19], peritonitis [53, 63, 64], vaginitis [65–68], esophagitis [54, 69, 70], urinary tract infection [55, 71], cellulitis [72], unexplained fever, or septic shock [56]. *S. cerevisiae* has also been associated with Crohn disease, and the presence of antibodies against this microorganism is considered to be a sensitive (50%) and specific (90%) diagnostic test [73–76]. The microorganism has also been described in patients with asthma [77], ulcerative colitis, and diarrhea [78].

However, the most important clinical syndrome caused by *S. cerevisiae* is fungemia, because it is usually the most severe and well-proven clinical manifestation of the disease. *S. cerevisiae* fungemia has been described in immunosuppressed patients (19 patients [31%]) and critically ill patients (28 [46%]), but also in relatively healthy hosts. Underlying conditions include cancer [17, 19], HIV infection [16, 40, 46], use of corticosteroids [31, 78], neutropenia [19, 20, 29, 35], bone marrow transplantation [22, 27, 52], solid organ transplantation [46],

burns [14, 25], and heart surgery [10, 26, 35, 38, 43–45]. Critically ill neonates seem to be particularly predisposed to fungemia [20, 32, 33, 35, 36, 42, 43, 47].

Five patients with *S. cerevisiae* fungemia were found to have infectious endocarditis (including our case) [10, 26, 38, 39, 43]. Two of the 5 patients died. We have also identified a patient with infection of an aortic-bifemoral graft who developed aorto-enteric fistula and finally died of the infection [44].

Therapy for *S. cerevisiae* fungemia should rely on the withdrawal of the probiotic preparation, if it was being given, administration of an antifungal agent, and, as with other types of fungemia, withdrawal of central venous catheters [45, 48]. Persistent fungemia in patients with incomplete removal of prosthetic materials has been reported [32, 48].

The antifungal agent of choice has not been established. *S. cerevisiae* has been consistently susceptible to amphotericin B (MIC_{90}, 0.5–1 μg/mL) and fluorocytosine (MIC_{90}, 0.25 μg/mL), whereas different rates of resistance to fluconazole and itraconazole have been reported [41, 52, 79, 80]. The isolates exhibited in vitro resistance to itraconazole (MIC, 1–16 μg/mL), and the MIC_{90} to fluconazole was 8–128 μg/mL. We tested our 4 isolates and found that the most potent antifungal compounds in vitro were flucytosine and voriconazole, with MICs of $\leqslant$0.25 μg/mL. Besides, no therapeutic failure has been clearly attributable to resistance, even in strains with reduced susceptibility to fluconazole (MIC, 32 μg/mL) [40], although cases of fungemia occurred in patients receiving fluconazole or ketoconazole [29, 35].

Until more data are available, the antifungal agent of choice seems to be amphotericin B. However, this does not imply, in our opinion, the impossibility of treating patients with fluconazole, because most MICs obtained for this drug are within the susceptibility range, and many successful results obtained with fluconazole have been reported in the literature (table 1). Despite the fact that data are scarce, both posaconazole and voriconazole have been reported to have good in vitro activity against this fungus [81–85].

The mortality rate for patients with *S. cerevisiae* fungemia was 29.5% (18 patients), although, in most cases, mortality could not be only attributed to fungemia. However, septic shock has been reported in patients with *S. cerevisiae* fungemia as a single isolate [36, 40], and Piarroux et al. [48] described a patient who died of sepsis even though *Saccharomyces* was the only microorganism isolated from blood cultures.

S. cerevisiae should not be dismissed as a nonpathogenic microorganism when recovered from a clinical source. A history of intake of health food supplements or probiotics should be investigated.

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