Review article

Saccharomyces boulardii as an agent of systemic infection: an integrative review

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SUMMARY

Objective: To analyze possible cases of infection by *Saccharomyces boulardii* worldwide from 2018 to 2023. **Methodology:** An integrative review was conducted using the Virtual Health Library, PubMed, and ScienceDirect databases, with the descriptors "probiotics", "*Saccharomyces boulardii*", and "fungemia," resulting in 11 articles. **Results:** A total of 69 cases of fungemia were identified in patients aged 3.5 to 93 years, with a mean age of 62 years and a male predominance. The main risk factors included antibiotic use, central venous catheterization, cancer, enteral nutrition, intensive care unit admission, and intubation. The most used antifungal was fluconazole. The fatality rate was 36.2%. **Conclusion:** Although probiotics containing *Saccharomyces boulardii* are generally used for their beneficial effects, it was found that, under certain circumstances, they may cause adverse events in some individuals. Therefore, the risk-benefit ratio should be carefully evaluated in each case.

Keywords: Invasive fungal infections; probiotic; fungemia.

RESUMO

***Saccharomyces boulardii* como agente de infecção sistêmica: uma revisão integrativa**

Objetivo: Analisar possíveis casos de infecção por *Saccharomyces boulardii* no mundo, no período de 2018 a 2023. **Metodologia:** Realizou-se uma revisão integrativa, nas bases de dados Biblioteca Virtual em Saúde, PubMed e ScienceDirect, usando os descritores "probiotics", "*Saccharomyces boulardii*" e "fungemia", incluindo ao final 11 artigos. **Resultados:** Observaram-se 69 casos de fungemia em pacientes com idades de 3 anos e meio a 93 anos, com média de 62 anos, e prevalência para o sexo masculino. Os principais fatores de risco foram: uso de antibióticos, uso de cateter venoso central, câncer, em nutrição enteral, estar em unidade de terapia intensiva e intubados. O antifúngico mais utilizado foi o fluconazol. A taxa de letalidade foi 36,2%. **Conclusão:** Embora os probióticos contendo *Saccharomyces boulardii* sejam utilizados por seus efeitos benéficos, averiguou-se que, sob determinadas circunstâncias, podem ocasionar eventos adversos a alguns indivíduos, devendo o risco-benefício ser avaliado em cada caso.

Palavras-chave: Infecções fúngicas invasivas; probiótico; fungemia.

RESUMEN

***Saccharomyces boulardii* como agente de infección sistémica: una revisión integradora**

Objetivo: Analizar los posibles casos de infección por *Saccharomyces boulardii* a nivel mundial, entre 2018 y 2023. **Metodología:** Se realizó una revisión integrativa en las bases de datos Biblioteca Virtual en Salud, PubMed y ScienceDirect, utilizando los descriptores «probióticos», «*Saccharomyces boulardii*» y «fungemia», incluyendo finalmente 11 artículos. **Resultados:** Se observaron 69 casos de fungemia en pacientes de entre 3,5 y 93 años, con una edad media de 62 años y una mayor prevalencia en hombres. Los principales factores de riesgo fueron: uso de antibióticos, catéter venoso central, cáncer, nutrición enteral, ingreso en la unidad de cuidados intensivos e intubación. El antifúngico más utilizado fue el fluconazol. La tasa de letalidad fue del 36,2 %. **Conclusión:** Si bien los probióticos que contienen *Saccharomyces boulardii* se utilizan por sus efectos beneficiosos, se ha descubierto que, en determinadas circunstancias, pueden causar efectos adversos en algunas personas, y la relación riesgo-beneficio debe evaluarse caso por caso.

Palabras clave: Infecciones fúngicas invasivas; probiótico; fungemia.

1. INTRODUCTION

The normal human intestinal microbiota comprises a diverse group of microorganisms that inhabit the gastrointestinal tract, playing a crucial role in maintaining gastrointestinal health and providing systemic benefits to the body through various important functions, including immune modulation. This microbiota is established at birth and evolves throughout an individual's life, with its composition influenced by several factors, including medical conditions [1-3].

Maintaining balance in the composition of the intestinal microbiota, in terms of quantity and quality, is of utmost importance to avoid situations such as dysbiosis and systemic repercussions. This microbiota comprises a diverse array of microorganisms, including bacteria, archaea, protozoa, viruses, and fungi. Since they make up this ecosystem, some of these microbes are ingested in the form of probiotics for health benefits [1-3]. The term "probiotic" refers to products that contain live microorganisms that, when administered appropriately, can help restore the intestinal microbiota. The consumption of probiotics dates to ancient times, primarily through fermented foods [4, 5].

However, these products are not regulated and tested with the same rigor as allopathic medications, resulting in inconsistencies in their mechanisms of action and safety profiles. In terms of composition, these products are manufactured using various bacterial strains, with *Lactobacillus* being the most utilized. The most prevalent fungal strain found in these products is the yeast *Saccharomyces boulardii* [3-7].

Saccharomyces boulardii is a unicellular eukaryotic microorganism, commonly known as "baker's yeast" or "brewer's yeast," due to its historical use in sugar fermentation for food and beverage production. This fungus can colonize various body sites, including the skin, vaginal mucosa, respiratory tract, and digestive tract [8-10].

In the pharmaceutical industry, it is used as an ingredient to produce probiotics, which are ingested to prevent and treat various diarrheal disorders. They are widely used by elderly patients, children, and especially in Intensive Care Units (ICUs) [9-12].

Microorganisms that are part of the human microbiota, such as yeasts of the genus *Candida*, under certain circumstances like immunosuppression, whether due to chemotherapy, organ transplants, or HIV infection, can develop pathogenic potential, causing various infectious

conditions, ranging from vulvovaginal and oral candidiasis to systemic candidiasis. In this regard, this research aimed to analyze possible cases of infection by *Saccharomyces boulardii* worldwide from 2018 to 2023 [13].

2. METHODOLOGY

This study is an integrative literature review designed to compile and analyze data from publications spanning 2018 to 2023, to address the following guiding questions: What are the documented occurrences of systemic infection by *Saccharomyces boulardii*? What risk factors are associated with *Saccharomyces boulardii* infection? What is the lethality rate among affected individuals?

The literature search was conducted from November to December 2023 across the scientific databases PubMed, ScienceDirect, and the Virtual Health Library (BVS). Articles published in English, Spanish, and Portuguese were selected using the keywords "probiotics," "*Saccharomyces boulardii*," and "fungemia." The Boolean operator "AND" was applied in the following combination: Probiotics AND *Saccharomyces boulardii* AND Fungemia.

The selection of articles for this study was conducted in three stages. First, titles were reviewed to identify relevant studies. In the second stage, abstracts were read, and studies not addressing the proposed research questions were excluded. Finally, a thorough reading of the selected articles was conducted for data extraction. Studies without free full-text access or those cataloged repeatedly across databases were excluded from the final sample.

3. RESULTS AND DISCUSSION

After searching for works in the BVS, PubMed, and Science Direct databases, a thorough analysis of the literature found was conducted, resulting in 93 verified works. Initially, 14 studies were excluded due to duplication, resulting in 79 records for analysis.

Subsequently, of the 79 records, 61 studies were excluded after reviewing titles and abstracts, as well as removing publications that required payment for full-text access. This left 18 studies eligible for further assessment; however, 7 of these did not address the study's guiding question and were therefore excluded. As a result, 11 studies were included in this review. Figure 1 details the number of publications analyzed, and the databases used.

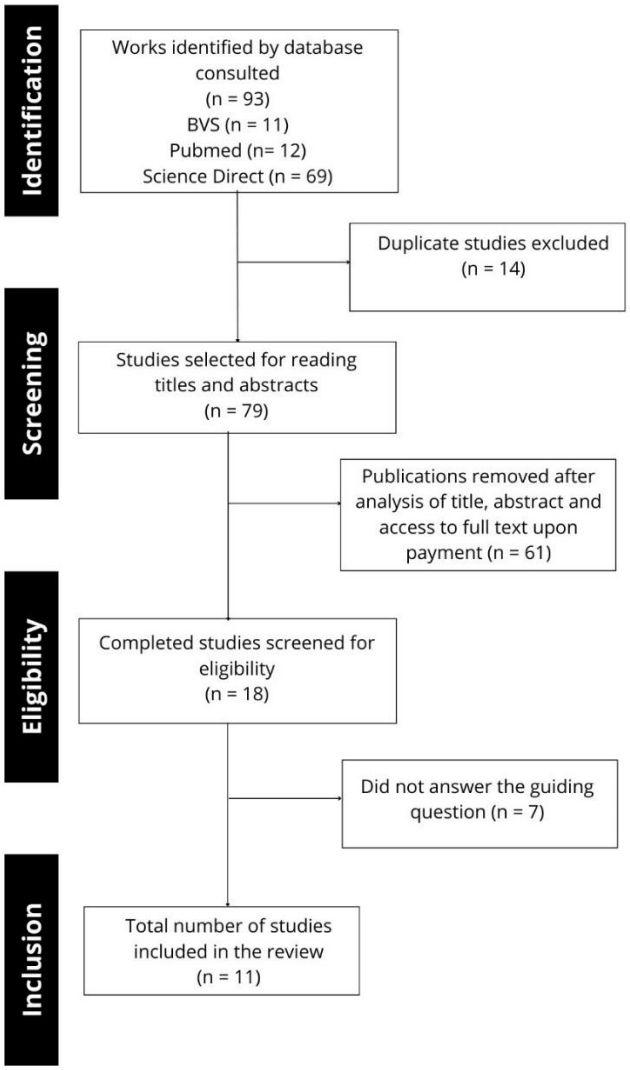

Figure 1. Flowchart illustrating the identification, screening, eligibility, and inclusion process for studies on cases of fungemia caused by *Saccharomyces cerevisiae* var. *boulardii* worldwide from 2018 to 2023.

Analysis of the articles selected in this integrative review enabled the collection of data to synthesize and deepen the understanding of the subject. This facilitated the acquisition of information regarding the clinical profile of individuals affected by fungemia caused by *Saccharomyces cerevisiae* var. *boulardii* worldwide from 2018 to 2023, as summarized in Table 1. The table compiles information from the selected studies, including publication year, title, study country, patient demographics (sex and age), associated risk factors, clinical presentation, diagnostic tests, and mortality. All 11 included studies were published in English. Most studies originated from India (three studies), followed by Turkey and the United States, with two studies each. Most publications were from 2019.

Table 1. Cases of fungemia caused by *Saccharomyces cerevisiae* var. boulardii worldwide from 2018 to 2023.

	Authors, year of publication / article title / study location	**Age – Sex**	**Possible observed risk factors**	**Clinical presentation**	**Death**
1	Kara *et al.*, 2018 / *Saccharomyces cerevisiae* fungemia after probiotic treatment in an intensive care unit patient/ Turkey	88 years – M 38 years – F	• Both used antibiotics • Both patients went to the Intensive Care Unit (ICU) • Intubation: 1 of 2 • Mechanical ventilation: 1 of 2.	• Both used the probiotic containing *Saccharomyces cerevisiae* var. *boulardii* and had positive blood cultures for the fungus.	1(F)
2	Chakravarty, Parashar, Acharyya, 2019 / *Saccharomyces cerevisiae* sepsis following probiotic therapy in an infant/ India	35 years – M	• Use of antibiotics • Admission to the ICU.	• Hospitalized with complaints of watery diarrhea • Malnourished and dehydrated • Used the probiotic containing *Saccharomyces cerevisiae* var. *boulardii*, 250 mg twice a day for 10 days • Erythematous macular rashes on the trunk and limbs • Lymphadenopathy • White blood cell count of 3.4×10^3 /µL with 2.52×10^3 /µL of neutrophils, hemoglobin level of 11.4 g/dL • Enlarged liver without splenomegaly • Lymphadenopathy • Slightly elevated C-reactive protein (CRP) • Blood culture positive for the fungus • Combined T and B cell deficiency	Not reported

Authors, year of publication / article title / study location		Age – Sex	Possible observed risk factors	Clinical presentation	Death
3	Gupta, Singh, Taneja, 2019 / *Saccharomyces*: A Friend or Foe in ICU (A Case Report with Solution)/ India	77 years – F	• Use of antibiotics • Admission to the ICU • Use of a central venous catheter • Diabetes • Intubation.	• Uncontrolled diabetes • Hypertension • Chronic obstructive airway disease • Diagnosis of bilateral pneumonia • Acute kidney injury • Used the probiotic containing *Saccharomyces cerevisiae* var. *boulardii* • Blood culture positive for the fungus	The patient passed away 24 days after admission
4	Chakravarty, Parashar, Acharyya, 2019 / *Saccharomyces cerevisiae* sepsis following probiotic therapy in an infant/ India	88 years – M 38 years – F	• Use of antibiotics • Admission to the ICU.	• Hospitalized with complaints of watery diarrhea • Malnourished and dehydrated • Used the probiotic containing *Saccharomyces cerevisiae* var. *boulardii*, 250 mg twice a day for 10 days • Erythematous macular rashes on the trunk and limbs • Lymphadenopathy • White blood cell count of 3.4×10^3 /μL with 2.52×10^3 /μL of neutrophils, hemoglobin level of 11.4 g/dL; • Enlarged liver without splenomegaly • Lymphadenopathy • Slightly elevated C-reactive protein (CRP) • Blood culture positive for the fungus • Combined T and B cell deficiency	Not reported

Clinical presentation	Death	Authors, year of publication / article title / study location		Age – Sex	Possible observed risk factors	Clinical presentation	Death
Underlying conditions/organs/system compromised: • Digestive tract: 27 of 46 • Neurological: 11 of 46 • Cardiovascular: 8 of 46 • Solid tumor with metastasis: 6 of 46 • Diabetes mellitus (any type): 6 of 46 • Pulmonary: 5 of 46 • Liver: 4 of 46 • Rheumatism: 4 of 46 • Chronic kidney failure: 3 of 46 • 10 did not report the use of the probiotic containing *Saccharomyces cerevisiae* var. *boulardii*, but all had a positive blood culture for the fungus	17	5	Landaburu *et al*., 2020 / Fungemia following *Saccharomyces cerevisiae* var. *boulardii* probiotic treatment in an elderly patient/ Argentina	82 years – F	• Use of antibiotics • Diabetes.	• Alzheimer, hypertension, and diabetes • Hospitalized for the placement of a feeding tube via gastrostomy • Used the probiotic containing *Saccharomyces cerevisiae* var. *boulardii*, 200 mg per day for 6 months • White blood cell count of 13.8 × 10^3 /μL and 12 × 10^3 /μL of neutrophils, platelet count 309 × 10^3 /μL, hemoglobin 11 g/dL • Blood glucose level of 134 mg/dL • Creatinine level of 0.44 mg/dL • Alkaline phosphatase (ALP) 119 U/L • Aspartate aminotransferase (AST) 44 U/L; alanine aminotransferase (ALT) 22 U/L • Blood culture positive for the fungus	None

Possible observed risk factors	Clinical presentation	Death	Authors, year of publication / article title / study location		Age – Sex	Possible observed risk factors
• Use of antibiotics: 3 of 10 • Admission to the Intensive Care Unit: 3 of 10 • Use of central venous catheter: 7 of 10 • Cancer: 3 of 10 • Parenteral nutrition: 3 of 10 • HIV: 1 of 10.	Underlying conditions/organs/compromised systems: • Digestive tract: 2 of 10 • Neurological: 2 of 10 • Cardiovascular: 2 of 10 • Pulmonary: 2 of 10 • All had used the probiotic containing *Saccharomyces cerevisiae* var. *boulardii* and had positive blood cultures for the fungus	5 (3 were male)	6	Rannikko *et al.*, 2021 / Fungemia and other fungal infections associated with use of *Saccharomyces boulardii* probiotic supplements/ Finland	30 years – F 39 years – 2(M) 40 years – M 42 years – 2(M) 45 years – M 52 years – 2(M) 55 years – M 56 years – M 58 years – F 59 years – M 60 years – 2(M) 63 years – M 66 years – M 67 years – 2(M)/2(F) 68 years – 2(M) 70 years – F 72 years – 3(F)/1(M) 75 years - F 76 years – F 77 years – 1(F)/1(M) 78 years – F 80 years – 1(F)/1(M) 83 years – 1(F)/1(M) 84 years – M 85 years – M 86 years – F 88 years – 1(F)/1(M) 91 years – 1(M)/1(F) 93 years – M	• Use of antibiotics: 33 of 46 • Use of central venous catheter: 9 of 46 • Cancer: 10 of 46 • HIV: 1 of 46.
• Use of antibiotics • Intubation.	• Closed fracture of the left humerus • After completing the antibiotics and resolution of *C. difficile* colitis, the patient presented with a fever of 41°C, along with altered mental status and nystagmus upon examination. She continued to experience persistent fevers for 24 hours • She had been using the probiotic containing *Saccharomyces cerevisiae* var. *boulardii* before hospitalization • Blood cultures were positive for the fungus	None				

Authors, year of publication / article title / study location		**Age – Sex**	Possible observed risk factors	**Clinical presentation**	**Death**	**Authors, year of publication / article title / study location**		**Age – Sex**
9	Gün *et al*., 2022 / *Saccharomyces cerevisiae* fungemia due to an unexpected source in the pediatric intensive care unit/ Turkey	6 years - M	• Use of antibiotics • Admission to the ICU • Intubation • Use of a central venous catheter • Cancer Use of probiotic by the patient next to him/her.	• Admitted to the ICU on the 14th day post-operation due to respiratory discomfort • Diagnosed with inoperable atypical rhabdoid/teratoid tumor • The patient next to him used the probiotic containing *Saccharomyces cerevisiae* var. *boulardii* • White blood cell count of 5.24 × 10^3 /μL, total neutrophils of 3.63 × 10^3 /μL, hemoglobin level of 9.6 g/dL, hematocrit of 28.4%, and platelet count of 652 × 10^3 /μL • Urea of 7 mg/dL; creatinine of 0.03 mg/dL • Sodium of 138 mmol/L, potassium 5 mmol/L, chloride 104 mmol/L, calcium of 8.1 mg/dL • C-reactive protein (CRP) of 11.3 mg/dL • Arterial blood gas was normal (pH: 7.39, HCO3: 21.8 mmol/L, pCO2: 37 mmHg) • Lactate of 1.6 mmol/L • Catheter tip culture positive for *Saccharomyces cerevisiae* var. *boulardii*	None	7	Poncelet *et al*., 2021 / *Saccharomyces cerevisiae* fungemia: Risk factors, outcome and links with *S. boulardii* - containing probiotic administration/ Belgium	21 years – M 34 years – M 40 years – F 53 years – M 55 years – M 59 years – F 80 years – M 82 years – 2(M) 88 years – F
						8	Shanmukhappa *et al*., 2022 / Unusual presentation of *Saccharomyces* fungemia after probiotics use in a critically ill patient with *Clostridium difficile* infection: a case report/ United States	51 years - F

	Authors, year of publication / article title / study location	Age – Sex	Possible risk factors observed	Clinical presentation	Death
10	Spiliopoulou *et al.*, 2023 / Fungemia due to rare non-*Candida* yeasts between 2018 and 2021 in a Greek tertiary care university hospital/ Greece	2 years – M 48 years – M 71 years – F	• Use of antibiotics; • Admission to the ICU.	• Patient aged 2 years - Diarrhea • Patient aged 48 years - Fabry disease, tetraplegia, gastrostomy, suprapubic catheter, prolonged stay in a rehabilitation facility • Patient aged 71 years - Respiratory failure, intubated, chronic heart failure, hypertension, dyslipidemia, obesity, and long-term hospitalization • Patient aged 2 years - Used the probiotic containing *Saccharomyces cerevisiae* var. *boulardii*; the others did not report using the probiotic containing the fungus • Hemocultures positive for the fungus	1 (F)
11	Tirlangi *et al.*, 2023 / *Saccharomyces* fungemia in two critically ill patients with acute pancreatitis/ India	20 years – M 27 years - F	• Use of Antibiotic: 2 of 2 • Mechanical ventilation: 1 of 2 • Parenteral nutrition: 1 of 2	• Pacient aged 20 years - Diagnosed with moderately severe acute pancreatitis with infected necrosis • Pacient aged 27 years - Severe acute pancreatitis and hospital-acquired pneumonia • Both used the probiotic containing *Saccharomyces cerevisiae* var. *boulardii* • Blood cultures positive for the fungus	Two patients

M: male; **F:** female. **Source:** Own authorship, 2024

During the study period, 69 cases of patients with *Saccharomyces cerevisiae* var. *boulardii* identified in blood or catheter tip cultures were reported, as shown in Table 1. According to the distribution of the reported cases, the patients ranged in age from 3.5 to 93 years, with an average age of 62 for both sexes. Regarding gender, 43(62%) of the patients were male. In the study by Rannikko *et al*. (2021) [12], which included a group of 46 individuals, comprising adults and the elderly of both sexes aged between 30 and 93 years, this higher frequency was also observed, with the majority being male (63%) as the most affected by fungemia. Likewise, Poncelet *et al*. (2021) [11] reported a higher proportion of cases in men, with an average age of 58 years, comparable to the present findings. Further studies are needed to evaluate a potential relationship between fungemia, gender, and age.

Regarding age, the group with the highest incidence of *Saccharomyces* fungemia cases was those over 60 years, representing 59.4% of affected individuals. Several studies indicate that the microbiota of this specific population differs from that of adults, as over time, there is a decrease in bacteria classified as beneficial and an increase in potentially pathogenic enterobacteria [14]. Moreover, excessive antibiotic use, whether combined with or independent of the aging process, can impact the homeostasis of the gut microbiota. As a result, functional foods, especially probiotics, are increasingly used by the elderly population [14]. According to Rannikko *et al*. (2021) [12], in hospitals in the United States, the probiotic containing *Saccharomyces cerevisiae* var. *boulardii* is commonly used, particularly among elderly patients.

The advantage of using a probiotic containing *Saccharomyces cerevisiae* var. *boulardii* is that it functions as an antidiarrheal biotherapeutic agent with proven benefits in various pathological conditions, particularly acute or chronic diarrhea. Unlike antibiotics, it does not alter intestinal morphology or microbiota and shows comparable efficacy to medications used for treating diarrhea. It inhibits the growth of enteric pathogens, can be used concurrently with antibiotics, and helps restore the natural balance of intestinal microbiota [15].

There is a report of a 74-year-old male patient who was admitted to the emergency room with symptoms of abdominal pain, chills, nausea, and vomiting. On the first day of hospitalization, the patient began antibiotic treatment, but no improvement was observed, making intubation and the insertion of a central venous catheter necessary. Blood cultures from days 1 and 2 showed *Saccharomyces* growth, although the patient had not used the probiotic containing *Saccharomyces boulardii* in the hospital. However, the patient reported prolonged use of the probiotic for 7 years before admission [9]. Regarding the use of the probiotic containing this yeast, it was observed that 81.2% of the patients who developed fungemia had used the probiotic. Of these, 29 reported using it at home, in nursing homes, outpatient clinics, or in the Intensive Care Unit (ICU). Among them, 25 individuals were using probiotics in the hospital when their blood cultures tested positive for *Saccharomyces*. Additionally, 48% did not specify where they had used the probiotic, and in one case, the patient had not used it at all.

In the last cited case, a 6-year-old male child was admitted to the ICU on the fourteenth day post-surgery due to respiratory discomfort, with an atypical rhabdoid/teratoid tumor. He was receiving antibiotics, intubated, and had a Central Venous Catheter (CVC). Although he did not use *Saccharomyces cerevisiae var. boulardii*, the culture from the catheter tip tested positive for the fungus on the twenty-fifth day of hospitalization in the ICU [5]. It was noted that this child had a spiky fever the day after a neighboring patient used the probiotic. This raised the possibility that transmission may have occurred through the hands of the ICU staff colonized with the strain.

In the case of the 6-year-old male child, hospitalized on the fourteenth postoperative day in the ICU, as reported by Gün *et al*. (2022) [5], several accounts describe cases of *Saccharomyces*

fungemia in hospitalized individuals who shared a room with patients using the yeast-containing probiotic. Gonsalez *et al*. (2023) [16] reports a potential risk associated with handling sachets and capsules containing the probiotic *Saccharomyces boulardii* in environments where patients are present, regardless of probiotic use. Studies have shown that viable strains can be detected up to one meter from the handling site and remain on surfaces for up to two hours. Thus, it is recommended that, for safety, probiotics be handled in a location distant from patients.

Reports indicate that this yeast can be found in the hands of individuals handling it without gloves, even after thorough handwashing. This presents a potential pathway for infection, which can occur through two primary mechanisms: contamination of the central venous catheter via the hands of healthcare professionals who handled the yeast or through airborne dispersion of strains following the handling of capsules or sachets. Additionally, infection may arise from the intestinal translocation of the ingested microorganism across the enteral or oral mucosa, with evidence suggesting that the risk of intestinal translocation is higher in elderly patients [5, 11, 16].

Some studies outline risk factors for *Saccharomyces* fungemia, noting patients in Intensive Care Units (ICUs) with central venous catheters, on mechanical ventilation, intubated, receiving total parenteral nutrition, using gastrostomy tubes, immunosuppressed due to medication or disease, with uncontrolled diabetes, cancer, prolonged hospital stays, undergoing broad-spectrum antibiotic treatment, or using the probiotic themselves or near other patients in the same unit who are also using it. Reports of *Saccharomyces* fungemia in previously healthy patients remain rare [10, 16-18].

Regarding the use of antibiotics, it was observed that 67% of patients were on these medications, 28% used Central Venous Catheters (CVC), 20% had some cancer, 17% were on enteral nutrition, 12% reported being in the ICU, 11% were intubated, and 6% were receiving total parenteral nutrition. Each of these factors, prolonged hospitalization, mechanical ventilation, HIV, and diabetes, accounted for 3%, while the use of probiotics by neighboring patients was reported in 1.5% of cases.

Saccharomyces should be considered a potential cause of nosocomial infection, as they share similar risk factors with other Healthcare-Associated Infections. These include antimicrobials, failure to adhere to basic control measures, inadequate hand hygiene, immunocompromised hospitalized patients, age over 60, prolonged hospitalization, and invasive medical devices such as central venous catheters, intubation, and mechanical ventilation [16-19].

Probiotics containing *Saccharomyces cerevisiae* var. *boulardii*, whether for treatment or prophylaxis, should be evaluated as a potential risk factor for nosocomial bloodstream infections in individuals with predispositions [16, 20, 21].

Additionally, some patients had prolonged use of the probiotic, including a 3.5-month-old infant who used it for 10 days, an 82-year-old patient who used it for 6 months, and a 74-year-old patient who used it for 7 years. According to a consultation with the electronic formulary of the Brazilian National Health Surveillance Agency (ANVISA), a duration of two to three days is sufficient for treatment. If symptoms persist after 5 days, reevaluation of the diagnosis and modification of therapy are recommended [8, 9, 17, 22].

The total number of deaths is illustrated in Figure 2, which indicates that 36.2% of patients affected by fungemia due to *Saccharomyces cerevisiae* var. *boulardii* died. Among these, 52% were men, with an average age of 72 years. The age group with the highest number of deaths was 60 years and older. When examining the number of deaths by sex and age group, among patients aged 19 to 59 years, 4 out of 7 death cases were female. In contrast, among patients aged 60 years and above, 10 out of 18 death cases were male.

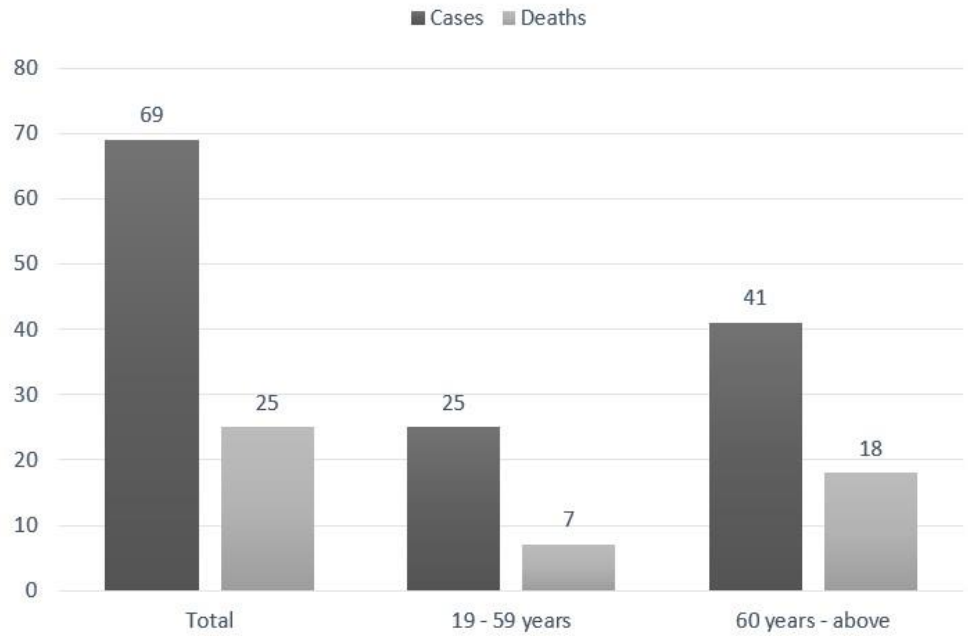

Figure 2. Number of deaths due to fungemia caused by *Saccharomyces cerevisiae* var. *boulardii* worldwide, categorized by age group, from 2018 to 2023.

As individuals' age and life expectancy increases, the immune system undergoes changes that increase susceptibility to various diseases, particularly after age 60. This process of immunosenescence has clinical implications, including increased susceptibility to infections, which contributes to higher morbidity and mortality rates in this population [23].

The occurrence and risk of infectious diseases are significant factors contributing to hospitalization and mortality, particularly in conjunction with advanced age. Furthermore, hospital-acquired infections represent a major cause of morbidity and mortality in the elderly population. A study involving a sample of 322 hospitalized individuals aged 60 years and older reported a mortality rate of 22.9% among patients with hospital-acquired infections [24]. According to the results presented in Figure 3, the distribution of fungemia cases by country varied significantly, with differing numbers of reports over various periods. Initially, Argentina and Spain had the lowest reported cases, with each country documenting only 1 case.

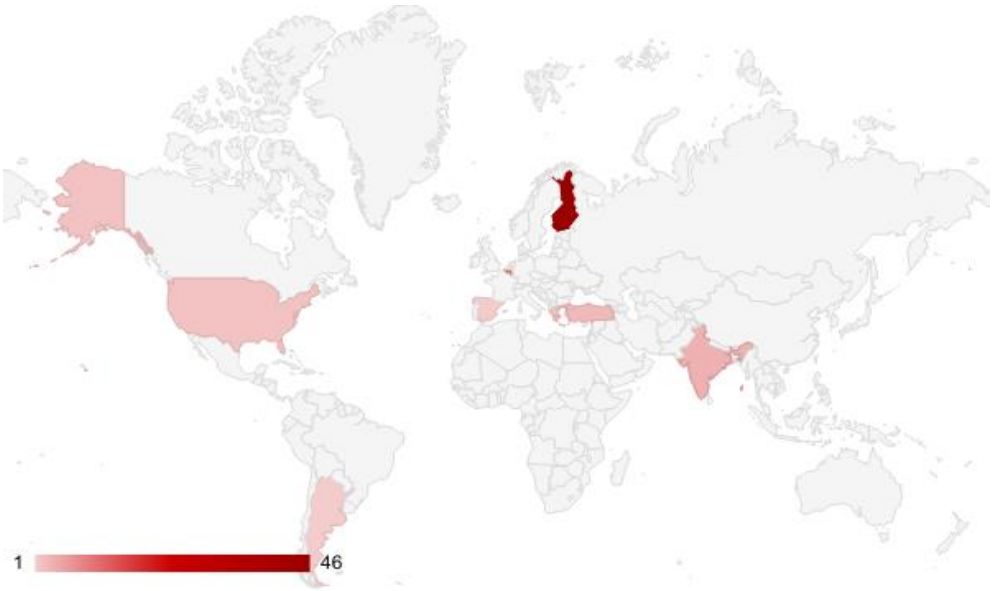

Figure 3. Geographic distribution of fungemia cases by *Saccharomyces cerevisiae* var. *boulardii* worldwide.

This is followed by the United States and Greece, which reported two cases each; Turkey with three cases; India with four reported cases; Belgium with ten occurrences between January 2005 and June 2017; and lastly, with the highest number of affected individuals, Finland with 46 cases of fungemia between January 2009 and December 2018.

The geographic distribution of cases has been explored in only a few studies that consider the number of countries worldwide. It is important to note that many additional cases may be occurring globally across various nations; however, due to a lack of diagnosis or misdiagnosis, this infection is likely underreported. Conversely, when cases are eventually identified, they may not reach the attention of researchers, who could subsequently disseminate such information through scientific publications on the topic.

As shown in Figure 4, the most used antifungal for the treatment of fungemia caused by *Saccharomyces cerevisiae var. boulardii* was fluconazole, with a total of 9 patients treated solely with this antifungal. It was followed by amphotericin B, which was used in 3 cases.

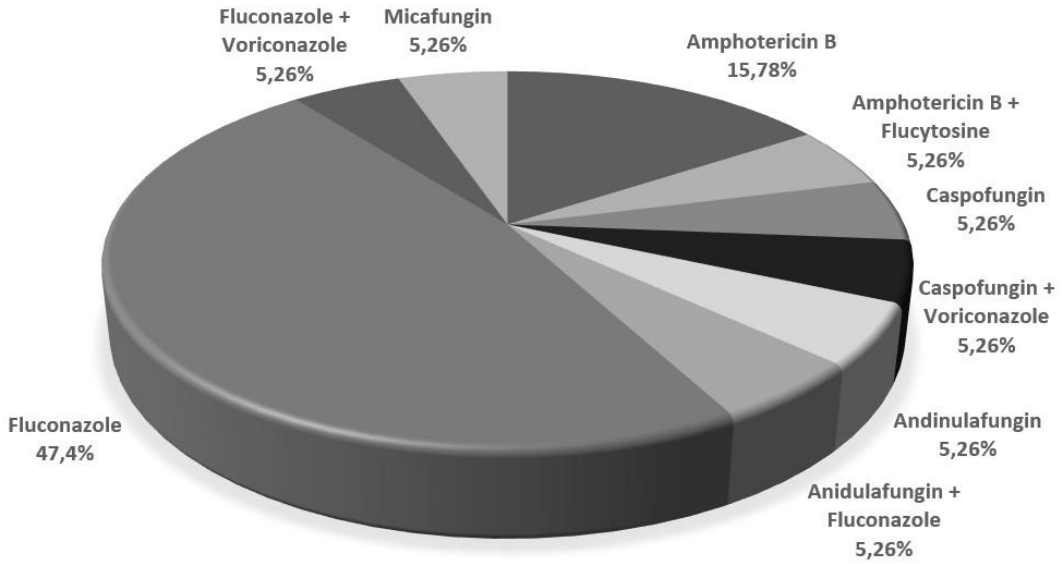

Figure 4. Antifungal agents utilized in the treatment of systemic infections caused by *Saccharomyces cerevisiae* var. *boulardii*.

It is important to note that anidulafungin was utilized in two treatments, one of which was administered concurrently with amphotericin B. Other antifungal combinations included amphotericin B combined with flucytosine. Voriconazole was also used in two treatments, both of which involved concurrent administration of another antifungal; in one instance, voriconazole was used alongside fluconazole, while in another, the patient received voriconazole in combination with caspofungin. Additionally, the treatment type for 46 patients was not specified, and in four cases, individuals did not receive any antifungal therapy, three of whom died, including two males aged 80 and 82 years.

Fluconazole, the most widely used drug, belongs to the azole class and inhibits ergosterol biosynthesis. It is indicated for the treatment of infections such as vaginal candidiasis, and balanitis, as well as for the prophylaxis of recurrent vaginal candidiasis and dermatophytosis like *Tinea pedis*, *Tinea corporis*, *Tinea cruris*, and *Tinea unguium*. Additionally, this antifungal has good pharmacokinetics, being well absorbed in the gastrointestinal tract without interference from gastric pH, and it has good penetration in all studied body fluids, such as cerebrospinal fluid, achieving a serum concentration of up to 70% [25, 26]. It is recommended that for the treatment of bloodstream infections associated with the use of probiotics, the central venous catheter should be removed, and either amphotericin B at a dose of 1 mg/kg/day or fluconazole at 10 mg/kg/day should be used, although there have been reports of strains resistant to both antifungals. Furthermore, studies have shown successful treatment cases of *Saccharomyces cerevisiae var. boulardii* with caspofungin [5].

Additionally, caution is advised when administering probiotics to patients with central venous catheters to prevent potential colonization. Measures such as hand hygiene, use of gloves, and avoiding probiotic handling near patients are recommended. Cases of fungemia have been reported in patients with central venous catheters, including those not receiving *Saccharomyces boulardii*, presenting with fever, and positive cultures for *Saccharomyces* [27].

4. CONCLUSION

The microorganisms that make up the human microbiota can exhibit pathogenic potential under certain conditions. Based on the findings of this research, 69 cases of patients affected by fungemia due to *Saccharomyces cerevisiae* var. *boulardii* were identified from 2018 to 2023.

Furthermore, it was possible to assess the clinical, laboratory, and sociodemographic profile of the affected patients, who had an average age of 62 years, predominantly male. The most common underlying conditions were related to the cardiovascular system, and the only laboratory findings that indicated similar abnormalities in the patients, aside from the positive cultures, were glucose levels, C-reactive protein, and low hemoglobin.

Regarding the observed risk factors, the five most prevalent were antibiotic use, central venous catheterization, cancer, enteral nutrition, and hospitalization in an Intensive Care Unit (ICU). The mortality rate was 36.2%, with the majority being male, particularly those over 60 years of age. Considering the risk factors for fungemia due to *Saccharomyces cerevisiae* var. *boulardii*, it is recommended to adopt certain precautions to prevent the emergence of complications. These include exercising caution when using probiotics containing *Saccharomyces boulardii* in elderly patients, those who are immunocompromised due to disease or medications, diabetics, cancer patients, individuals on antibiotics, those in intensive care, using central venous catheters, intubated, on mechanical ventilation, hospitalized for extended periods, re-

ceiving parenteral nutrition, and those with gastrostomy tubes. Furthermore, capsules and sachets containing the probiotic *Saccharomyces boulardii* should be handled in a separate environment, away from patient rooms, with gloves being changed after each manipulation.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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