

Can use of probiotics drugs cause fungemia? – a literature review

O uso de medicamentos probióticos pode causar fungemia? – uma revisão da literatura

¿El uso de medicamentos probióticos puede causar fungemia? - una revisión de la literatura

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Abstract

Commercially, there are many products sold as probiotics composed by *Sacharomyces boulardii*, with probiotic drugs being those that are widely used in different clinical situations. The probiotic efficacy of these agents is proven in many studies, as well as their safety in normal use situations. However, there have been some reports of fungemias related to the use of these probiotics in hospitals associated with some factors. Therefore, our objective is to review the knowledge about this association, focusing on the factors that provide it and the development mechanisms. For the development of fungemia associated with the use of probiotics, it is observed that it has greater development potential in patients using a central venous catheter. Although this is the main factor, others that reduce the patient's immune status, as well as reduce the intestinal defense barriers, contribute to this process, increasing the risk of fungemia. Despite the well-documented benefits of probiotics, their use must be carefully evaluated for each patient, due to factors that contribute to associate the use of probiotic drugs with the risk of developing bloodstream infection by *S. boulardii*. It is necessary, therefore, to include protocols that generate alerts about this risk and establish preventive measures.

Keywords: Probiotics; *Saccharomyces boulardii*; Fungemia; Immunocompromised Host.

Resumo

Comercialmente, existem muitos produtos vendidos como probióticos compostos por *Sacharomyces boulardii*, sendo os probióticos os medicamentos mais utilizados em diversas situações clínicas. A eficácia probiótica desses agentes é comprovada em muitos estudos, bem como sua segurança em situações normais de uso. No entanto, existem alguns relatos de fungemias relacionadas ao uso desses probióticos em hospitais associados a alguns fatores. Portanto, nosso objetivo é revisar o conhecimento sobre essa associação, focando nos fatores que a propiciam e nos mecanismos de desenvolvimento. Para o desenvolvimento de fungemia associada ao uso de probióticos, observa-se um maior potencial de desenvolvimento em pacientes em uso de cateter venoso central. Embora este seja o principal fator, outros que reduzem o estado imunológico do paciente, assim como a redução das barreiras de defesa intestinais, contribuem para esse processo, aumentando o risco de fungemia. Apesar dos benefícios bem documentados dos probióticos, seu uso deve ser cuidadosamente avaliado para cada paciente, devido a fatores que contribuem para associar o uso de medicamentos probióticos ao risco de desenvolver infecção da corrente sanguínea por *S. boulardii*. É necessário, portanto, incluir protocolos que gerem alertas sobre esse risco e estabelecer medidas preventivas.

Palavras-chave: Probióticos; *Saccharomyces boulardii*; Fungemia; Hospedeiro Imunocomprometido.

Resumen

Comercialmente, existen muchos productos vendidos como probióticos compuestos por *Sacharomyces boulardii*, siendo los probióticos los fármacos más utilizados en diversas situaciones clínicas. La eficacia probiótica de estos agentes está demostrada en numerosos estudios, así como su seguridad en situaciones de uso normal. Sin embargo, existen algunos reportes de fungemia relacionada con el uso de estos probióticos en hospitales asociados a algunos factores. Por tanto, nuestro objetivo es revisar el conocimiento sobre esta asociación, centrándonos en los factores que la favorecen y los mecanismos de desarrollo. Para el desarrollo de fungemia asociada al uso de probióticos, existe un mayor potencial de desarrollo en pacientes usuarios de catéteres venosos centrales. Si bien este es el principal factor, otros que reducen el estado inmunológico del paciente, así como la reducción de las barreras de defensa intestinales, contribuyen a este proceso, aumentando el riesgo de fungemia. A pesar de los beneficios bien documentados de los

probióticos, su uso debe evaluarse cuidadosamente para cada paciente, debido a factores que contribuyen a asociar el uso de medicamentos probióticos con el riesgo de desarrollar infección del torrente sanguíneo por *S. boulardii*. Por ello, es necesario incluir protocolos que generen alertas sobre este riesgo y establecer medidas preventivas.

Palabras clave: Probióticos; *Saccharomyces boulardii*; Fungemia; Huésped Inmunocomprometido.

1. Introduction

The use of probiotics for health maintenance has records that go back to the Old Testament, in which Abraham's longevity was associated with the consumption of sour milk (Schrezenmeir & De Vrese, 2001). Despite this, only at the beginning of the last century, there was a correlation between the microorganisms existing in these foods and the health benefits. This proposal was produced by the Russian immunologist Elie Metchnikoff, winner of the Nobel Prize, in which the increase in longevity caused by fermented milk was due to the exchange of pathogenic intestinal microorganisms by food lactobacilli (Gordon, 2008). Later, two American researchers brought to the scientific community a definition for the term probiotics, these being "growth-promoting factors produced by microorganisms" (Lilly & Stillwell, 1965).

In 2001, a second definition of what would be probiotics was proposed by the Food and Agriculture Organization of the United Nations (FAO) in conjunction with the World Health Organization (WHO). This new concept determined that "probiotics are living microorganisms that, when administered in adequate quantities, confer a benefit on the health of the host", and since then, several authors have found similar concepts (Food and Agriculture Organization - World Health Organization, 2002).

Among the existing probiotics, many formulations contain yeast, and these products are composed of *Saccharomyces boulardii*, because this yeast species being the only one, among other tested fungi, to have probiotic effects in clinical trials (Sazawal et al, 2006, Guimarães et al, 2018). Commercially, there are many products sold as probiotics composed of *S. boulardii*, such as fermented vegetables and yogurts (Lourens-Hattingh & Viljoen, 2001, Sindhu & Khetarpaul, 2002) and the presentation in freeze-dried capsules or heat-dried preparations are the most common (McFarland, 2010, Tomičić et al, 2016).

These probiotic agents act in several clinical situations, such as preventing diarrhea associated with the use of antibiotics, treating diarrhea and recurrent colitis due to *Clostridium difficile*, diarrhea of "travelers", acute diarrhea of bacterial and viral etiology and inflammatory bowel disease or syndrome irritable bowel, in addition to supplementing hydration in adults and children (Czerucka et al, 2007, Goldin & Gorbach, 2008, Im & Pothoulakis, 2010, Vandenplas et al, 2015). Although the probiotic efficacy of these agents has been proven in many clinical studies, as well as their safety in normal use situations (McFarland & Bernasconi, 1993, Acevedo et al, 2003, Buts & Bernasconi, 2005, Graf & Gavazzi, 2007), there have been some reports of fungemias related to the use of these probiotics (Muñoz et al, 2005, Belet et al, 2005, Didari et al, 2014, Kara et al, 2018).

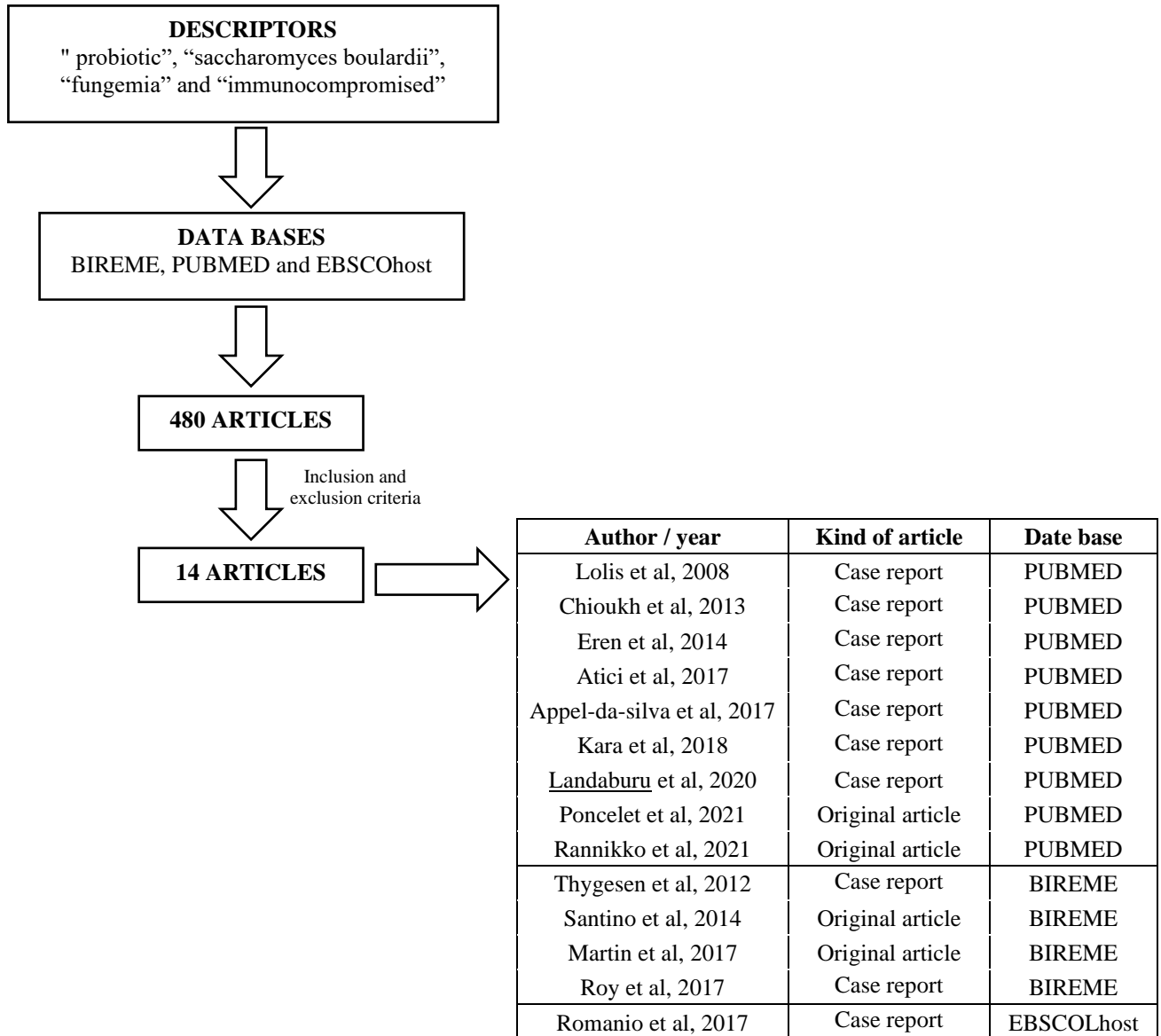
Fungemia incidence by *S. boulardii* is still unknown, although population-based studies suggest that it is responsible for 0.1 to 3.6% of all episodes of fungemia (Thygesen et al, 2012). Several studies report that this infection occurred in patients with a history of using probiotics or evidence of acquisition in an environment where probiotics were used (Perapoch et al, 2000, Atıcı et al, 2017). In this context, this review seeks to update the knowledge about this association, focusing on the factors that provide it, the mechanisms of development and its prevention.

2. Methodology

This study consisted of a literature review with data collection through a bibliographic survey in the BIREME, PUBMED and EBSCOhost databases, using the descriptors "Probiotic", "*Saccharomyces boulardii*", "Fungemia" and "Immunocompromised host" combined with each other. through the Boolean operator "AND". After the search, the inclusion

criteria (articles published in Portuguese, English or Spanish; full-length articles that portray the theme; and articles published between 2008 and 2021) and exclusion criteria (review articles and repeated publications) were applied.

Table 1.



Source: Authors.

3. Results and Discussion

3.1 Use and safety of probiotics in the therapeutic scheme

Probiotics are used in healthy populations, as well as at-risk populations (with different diseases), is considered beneficial for both. Although the mechanisms that provide its clinical benefits are not well understood, some hypotheses shed light for renewing the microbiota of the gastrointestinal tract (GIT) through maintenance and protection of the intestinal epithelium, the reduction of inflammation and modulation of the individual's immune profile (Kotharia et al, 2019).

The inclusion of probiotics in the therapeutic regimen of at-risk populations, in most cases, is related to the treatment or prevention of some gastrointestinal disorder. Among the disorders that justify the use of the probiotic, it is possible to

highlight diarrhea due to the imbalance of the intestinal microbiota caused by the use of broad-spectrum antibiotics (Lolis et al, 2008, Eren et al, 2014, Appel-da-Silva et al, 2017, Roy et al, 2017, Kara et al, 2018), diarrhea associated with *Clostridium difficile* (Santino et al, 2014, Kotharia et al, 2019) and diarrhea without a defined cause (Atıcı et al, 2017). In addition, they can be used in prophylactic therapy for *C. difficile* infection associated with antibiotics (Martin et al, 2017) and in cases of hospitalized premature newborns (Chioukh et al, 2013, Roy et al, 2017).

3.2 Use of probiotics and fungemia

Hematogenous fungemia or fungal infection corresponds to the presence of fungi in the bloodstream (Do Couto et al, 2011) and is considered an important public health problem, with high mortality, around 29% (Muñoz et al, 2005, Fadhel et al, 2019), mainly in immunocompromised patients (Cassone et al, 2003, Thygesen et al, 2012).

One of the first cases of *S. cerevisiae* fungemia, a species that previously included the *S. boulardii* species, was described in 1980, in a 59-year-old patient from Louisiana, United States, who suffered burns and was treated with hyperalimentation (including probiotic use) (Eschete & West, 1980). As of this date, several other cases (Lolis et al, 2008, Thygesen et al, 2012, Chioukh et al, 2013, Eren et al, 2014, Santino et al, 2014, Appel-da-Silva et al, 2017, Atıcı et al, 2017, Martin et al, 2017, Romano et al, 2017, Roy et al, 2017, Kara et al, 2018, Landaburu et al, 2020, Poncelet et al, 2021, Rannikko et al, 2021) reinforced the correlation between the microorganism that makes up probiotic drugs and those present in samples of patients with fungemia. Despite this, microorganism origin confirmation is necessary to adequately suggest the association. This is one of the main limitations of many studies.

To confirm this correlation, molecular techniques that allow the comparison of the genetic identity between the microorganisms studied, characterizing them as they or not, must be performed. Sequencing is one of the main tools for this end, and pulsed-field gel electrophoresis (PFGE) or analysis of nuclear and mitochondrial DNA restriction by endonuclease can also be used (Martin et al, 2017). Recently, Imre, et al. (2019) developed a fast and reliable multiplex PCR protocol for the identification of fungal infection sources by *S. boulardii* based on a combined analysis of interdelta fingerprinting and microsatellite typing.

However, few studies carry out molecular tests to prove the association, such as Lolis et al. (2008) and Martin et al. (2017), who found a high similarity (> 95%) between the microorganism isolated from the patient and those presenting in probiotic drug, by sequencing the ITS region and the D1 / D2 of the ribosomal DNA, and the profile proteomics by MALDI-TOF.

3.3 Risk factors for fungemia in the use of probiotics

Although the use of probiotic drugs composed of *S. boulardii* is recommended by international protocols, their safety is compromised in some situations, such as severe systemic gastrointestinal disease (Santino et al, 2014, Roy et al, 2017), treatment with broad-spectrum antibiotics (Lolis et al, 2008, Eren et al, 2014, Rannikko et al, 2021), use of mechanical ventilation or central venous catheter (Thygesen et al, 2012, Atıcı et al, 2017, Kara et al, 2018), use of immunosuppressive drugs and immunocompromised states, including advanced age (Chioukh et al, 2013, Martin et al, 2017, Romano et al, 2017, Poncelet et al, 2021). Despite the existence of these risk factors, the precautions established in the package inserts of most probiotic drugs include only patients using a central venous catheter (CVC) (EMS Sigma Pharma LTDA, 2014, Brainfarma Indústria Química e Farmacêutica, 2015, Merck, 2015).

Although other factors have been observed, CVC use is still the predominant risk factor. It is the port with the greatest potential for contamination of the patient's blood by microorganisms present in the probiotic drug, despite studies have found

negative tip catheter cultures (Thygesen et al, 2012, Chioukh et al, 2013, Santino et al, 2014). This lack of pathogen isolation can be explained by the variation in the microbial load in the blood as a consequence of its life cycle.

The potential for contamination related to the CVC use happens by the proximity of this device to the oral cavity. This often occurs through the hands of health professionals who manipulate the medication during administration or by aerial dispersion of the medication containing the microorganisms after opening the capsules or sachets with the lyophilized medication (Venugopalan et al, 2010). The presence of a nasogastric tube presents itself as a factor that further helps contamination, given that for the administration of the drug, it is necessary to open the capsules to prepare the solution to be administered by the tube (Thygesen et al, 2012, Romano et al, 2017). The issue of opening the capsules is of concern during administration in wards, especially near to patients using CVC, as it is reported that the probiotic agent *S. boulardii* remains viable for two hours, at a distance of one meter and can be found in caregivers' hands, even after vigorous washing with soap (Chioukh et al, 2013). This also leads to patients contamination who are not using the probiotic medication, but who are close to the patient who is being treated with this medication or who are handled by the same health professionals.

Another route of considerable contamination is related to the intestinal tract since it is the body's site most colonized by a complex community of microbes. The microbial consortium is critical for human health, having been involved in the development of the immune system, energy homeostasis and protection against pathogens, among other processes (Neish, 2009, Sekirov et al, 2010, Antunes et al, 2011). Therefore, its imbalance, such as caused by the broad-spectrum antibiotics use or serious gastrointestinal diseases, favor the adhesion and permanence of microorganisms that do not belong to the microbiota or that are part of the transient microbiota (Sekirov et al, 2008, Lawley et al, 2009, Sekirov & Finlay, 2009, Antunes et al, 2011). This process is the first step towards the development of intestinal infections and the process of enteral translocation. Translocation is the main route of microorganisms transmission present in the intestine into the bloodstream, being one of the pathways considered for the fungemia development by *S. boulardii* originating from probiotic drugs. The use of immunosuppressants, as well as immunocompromised situations, increases the risk of translocation occurring even by microorganisms considered non-pathogenic (Thygesen et al, 2012).

3.4 So what to do?

Knowledge of the patient's clinical status is extremely important for the safe use of probiotic drugs. Regardless of the specific conditions, patients, in all situations under study, were hospitalized. According to the US Food and Drug Administration (FDA) (2013) (Doron & Snyderman, 2015), inpatients are considered a potential risk group for the development of fungemia with the use of probiotics, including also pregnant women, patients with disease structural heart disease and those with the greatest potential for translocation of probiotic microorganisms through the intestinal wall. All of these factors are directly or indirectly related to immunocompromised situations. With the lowered immune status, either by the use of immunosuppressants or by clinical situations that generate immunocompromise, the individual cannot prevent the development of the microorganism in the bloodstream when the contamination is direct through the catheter or the translocation of the microorganisms from the intestine to the bloodstream (Galeev et al, 2009, Ypsilantis et al, 2010, Doron & Snyderman, 2015, Romano et al, 2017).

Institutional guidelines are needed to address possible safety issues related to the use of *S. boulardii*, as well as the establishment of prophylactic measures. Following the decision to use probiotics based on careful risk assessment, it is suggested that the following measures be taken: healthcare professionals should wear gloves when handling probiotic agents for administration, promptly dispose of them and properly wash their hands with water and soap; if it is necessary to prepare the lyophilized medication or to open the medication capsules for administration via the tube, these should not be carried out in separate rooms from the wards (Venugopalan et al, 2010).

4. Conclusion

Despite the well-documented benefits of probiotics, their use must be carefully evaluated for each patient, due to the association between the probiotic drugs use and the risk of developing bloodstream infection. As noted in this review, patients using CVC are the individuals most exposed to risk, however, other factors that lead to a decrease in the patient's immune status further increase this risk. Therefore, it is necessary to use the information described here to establish protocols that describe precautions related to these risk factors and measures to prevent contamination related to the administration of probiotic medication and manipulation in individuals more prone to the development of fungemias.

Although the studies suggest a relationship between the presence of fungemia and the risk factors described, further studies are needed to deepen the investigation of the mechanisms directly related to the development of fungemia and the use of probiotic drugs. Understanding these mechanisms would allow the development of prophylactic measures, including studies on the effectiveness of these actions, as well as more studies that address the risks and benefits of using probiotic drugs.

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