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A Unique Clinical Presentation of an Emerging Invasive Fungal Infection in a Hospitalized Patient: the Lessons Learned

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Abstract Invasive *Saccharomyces cerevisiae infection* is a rare and emerging fungal infection. The emergence of this invasive infection is due to the increased use of *Saccharomyces boulardii* probiotics. *Saccharomyces boulardii* probiotics are biotherapeutic agents used for the prevention and treatment of various diarrheal diseases. The benefits of these probiotics are well established; however, its associated infectious complications seem underestimated, especially in at-risk patients. Like other rare invasive yeast infections, invasive Saccharomyces infection has a high mortality rate. A 67-year-old man with multiple medical comorbidities and a complicated hospital course received *Saccharomyces boulardii* probiotics via percutaneous endoscopic gastrostomy tube for 22 days for *Clostridium difficile* prophylaxis treatment. We diagnosed him with invasive *Saccharomyces cerevisiae* fungemia resulting from *Saccharomyces cerevisiae* peritonitis. He developed multiple organ failure and shock, which led to his death 27 days after his first dose of *Saccharomyces boulardii* probiotics. To the best of our knowledge, we report the first case of invasive *Saccharomyces cerevisiae* fungemia due to *Saccharomyces cerevisiae* peritonitis caused by the combination of percutaneous endoscopic gastrostomy (PEG) tube placement and PEG tube administration of *Saccharomyces boulardii* probiotics in an at-risk hospitalized patient. Our goals for reporting this case are to heighten the index of clinical suspicion of invasive *Saccharomyces* fungemia, discuss the lessons we learned, and revisit the literature on the management of invasive *Saccharomyces* infection in at-risk hospitalized patients.

Keywords: *invasive Saccharomyces cerevisiae, emerging fungal infection, Saccharomyces boulardii probiotics, Saccharomyces cerevisiae fungemia, Saccharomyces cerevisiae peritonitis, transmigration, hospital-acquired transmission*

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1. Introduction

Saccharomyces boulardii (*S. boulardii*) is a yeast used in some commercial probiotic preparations and dietary supplements [1]. This live organism was believed to be nonpathogenic [2]. While the benefits of *S. boulardii* as probiotics are well established, these probiotics are not entirely risk -free. Emerging reports of *Saccharomyces cerevisiae* (*S. cerevisiae*) as an invasive pathogen exist in the literature [3,4,5,6].

We report a unique case of invasive *Saccharomyces cerevisiae* fungemia in a 67-year-old man. He had percutaneous endoscopic gastrostomy (PEG) tube placement and PEG tube administration of *Saccharomyces boulardii* probiotics before his diagnosis of *Saccharomyces cerevisiae* fungemia and peritonitis. We present this case in a chronological sequence of his three admissions at our hospital to emphasize his complicated hospital course.

2. Background

The progressive rise in invasive *Saccharomyces cerevisiae* infections is associated with the increase in the use of *Saccharomyces boulardii* probiotics [3,6]. This rare infectious complication is underreported, due to improper documentation and the lack of systematic reporting of probiotics adverse events. In 2018, a major research article reported only 93 cases of invasive *S. cerevisiae* infection [6]. The incidence of fungemia caused by *S. cerevisiae* is not known; however, few epidemiologic studies have quoted ranges of 0.1% to 3.6% of all episodes of fungemia [7,8,9].

The benefits of *S. boulardii* probiotics are recognized. Saccharomyces probiotic is used for acute gastrointestinal

diseases like *Clostridium difficile (C. difficle)* infection, enteral nutrition-related diarrhea, antibiotic-associated diarrhea, and acute diarrheal disease. Its benefits in most chronic diseases like Crohn's disease, ulcerative colitis irritable bowel syndrome and human immunodeficiency virus (HIV) related diarrheal disease are mostly inconclusive and more substantial studies are needed [2,10,11]. *Saccharomyces boulardii* is also found in some dietary supplements [1].

Saccharomyces cerevisiae (also called baker's yeast or brewer's yeast) is a non-spore forming fungus believed to be widespread in nature [12]. *Saccharomyces cerevisiae* colonizes the mucosal surfaces and is part of the normal flora of the gastrointestinal tract, the respiratory tract and the vagina [13]. The organism has colonized the respiratory tract of some patients with chronic pulmonary disease [14]. Recent studies have corroborated the current thinking that *S. boulardii* is identical to a particular strain of *S. cerevisiae*, contrary to previous thinking of *S. boulardii* being a subtype of *S. cerevisiae*. The presence of *S. cerevisiae* in the biological materials of patients treated with *S. boulardii* probiotic preparations is confirmatory [5,15,16]. Our case also supports this finding, as our patient developed invasive *S. cerevisiae* infection following the administration of *S. boulardii* probiotics.

Based on our review of the available literature, we observed that all the reported cases of invasive *Saccharomyces cerevisiae* had at least one underlying medical condition and at least one predisposing factor. The cited predisposing factors that seem to correlate with the development of *S. cerevisiae* fungemia are; the use of *S. boulardii* probiotic, parenteral or enteral nutrition, intravenous or indwelling catheter use, previous antibiotic use given at least 7 days prior to the diagnosis of Saccharomyces infection, adults over 60 years; intensive care unit stay due to critical illness; and neutropenic patients; absolute neutrophil count of less than 500cells/ microliter [5,4,8,17]. Cases of *S. cerevisiae* fungemia is also known in the pediatric age group, especially the critically ill and premature neonates [18,19,20,21,22].

The magnitude of invasive Saccharomyces infections in hospitalized patients can be massive. Cases of hospital-acquired transmission of *S. boulardii* were reported in hospitalized patients that received *S. boulardii* probiotics and also in patients that did not receive the probiotics [8,23,24]. The enteral administration of Saccharomyces probiotics requires opening the probiotic capsule before the administration of the viable yeast through enteral routes like a nasogastric tube or a PEG tube. This process can cause hand contamination of the staff or environmental contamination due to aerial transmission. Intravenous catheter insertion sites can be a portal of entry for Saccharomyces fungemia in the scenario of hand contamination [4,5,8,17].

Two studies strongly suggest that *S. cerevisiae* nosocomial transmission can occur in patients being in the vicinity of probiotic treated patients and person to person transmission, especially in closed units, through hand transmission, and environmental transmission [8,25]. The risk of nosocomial invasive Saccharomyces infection is another reason for healthcare providers to engage in stringent hand hygiene practices and proper disposal precautions.

Two other clinical scenarios worthy of mention are a case report of an otherwise healthy baker with no underlying chronic disease, and no other predisposing factors expect prolonged exposure to the viable fungus who was diagnosed with invasive disseminated *S. cerevisiae* infection [26].

The second scenario is a case report of invasive S. cerevisiae infection in an at-risk patient with no exposure to *S. boulardii* probiotics [27]. This case described the isolation of *S. cerevisiae* in the blood, urine, stool, and vaginal swab of a patient diagnosed with acute pyelonephritis due to renal calculi with Stage 5 chronic kidney disease and diabetes mellitus. This patient did not receive *S. cerevisiae* probiotics. The authors of the article postulated that there was the transformation of *S. cerevisiae* colonization into virulent organisms in the patient. They also suggested that the patient's renal calculi was the nidus for the development of her acute pyelonephritis, and uroepithelial disruption, which became the portal of entry and dissemination of *S. cerevisiae*, despite the absence of *S. boulardii* probiotics exposure in the patient.

3. Case Presentation

Our hospitalist service admitted a 67 - year-old man for worsening acute hepatic encephalopathy with an elevated ammonia level. He was discharged from a nearby hospital about 24 hours before his presentation to our emergency room. His notable medical comorbidities were alcoholic liver cirrhosis, untreated hepatitis C infection, marijuana use, and 1pack per week history of tobacco use.

Table 1. Hospital course for the patient's first admission

Hospital Activities	Hospital Day	Comments/ Outcome
Electroencephalogram (EEG)	Hospital day 7	Abnormal EEG showed slow background activity, no clear epileptiform activity
Urine Culture	Hospital day 11	Urine Culture reported as no growth
Blood Culture	Hospital day 11	Blood culture reported as no growth
Blood Culture	Hospital day 16	Blood Culture reported as no growth
ICU admission from the medical floor	Hospital day 19	Persistent hypothermia of 91.0- and 93.0-degrees Fahrenheit range and persistent lethargy
ICU downgrade to the medical floor	Hospital day 21	Lack of improvement of lethargy and hypothermia.
Discharge Day	Hospital day 28	The patient was discharged to a nursing home with hospice care and do not resuscitate code (DNR) status.

Admission # 1: Computerized tomography of his head and chest X-ray were unremarkable for acute processes. He did not have ascites on his abdominal ultrasound. The patient remained encephalopathic with intermittent delirium, hallucinations, and agitations despite improving ammonia level. Based on his abnormal electroencephalogram results and his risk for seizures, we started the patient on Keppra. His feedings were inconsistent because of his altered mental state. The consensus diagnosis was presumptive cortical dementia from alcohol abuse and synthetic

marijuana in the setting of hepatic encephalopathy. He required intensive care unit (ICU) care during the admission, and there was a delay in disposition to a nursing home due to his high level of nursing care requirements. We removed his intravenous catheter at the time of discharge to a nursing home. Table 1 summarizes the patient's first hospital course.

Table 2. Hospital course for the patient's second admission

Hospital Activities	Hospital Day	Comments/ Outcome
Blood Culture	Hospital day 1	Blood cultures results showed no growth
Cosyntropin Test	Hospital day 4	Relative adrenal insufficiency (RAI) diagnosed. Steroid treatment was started on hospital day 6 for RAI
Human Immunodeficiency Virus (HIV) screening test	Hospital day 8	HIV screening test was negative
Lumbar puncture performed	Hospital day 9	Neurosyphilis was diagnosed based on CSF. No evidence of bacterial meningitis.
Discharge Day	Hospital day 12	The patient was transferred to a higher level of care facility.

Admission #2: The patient was readmitted to our hospitalist service within 48 hours of his discharge to the nursing home for unresponsiveness, inadequate oral intake, and hypothermia of 93. 9 degrees Fahrenheit. The nursing home requested placement of a PEG tube for feeding as a requirement for his re-admission. The patient continued to have intermittent hypothermia, which required warming blankets as needed. Neurosyphilis was diagnosed based on his cerebrospinal fluid (CSF) analysis and specific syphilis serologies. The patient was started on a 14-day course of IV penicillin g 4 million every 4 hours. His mentation continued to wax and wean. We transferred him to a higher level of a care facility with infectious disease expertise for neurosyphilis treatment. He was unable to get a PEG tube placed before the transfer, despite his feeding challenges. Table 2 summarizes the patient's second hospital course.

Admission # 3: The patient was transferred back to our hospital to complete his treatment of neurosyphilis after a 7-day hospital stay at the higher level of care facility. His clinical condition progressively declined. He continued to have intermittent bradycardia and hypothermia due to possible adrenal insufficiency. He had also developed anasarca with ascites and acute renal failure suggestive of hepatorenal syndrome. His blood urea nitrogen and creatinine level worsened from 14.5 mEq/L (6.0 - 19mq/dl) and 0.78 (0.7 - 1.6mq/dl) respectively to 109.6mEq/L, and 5.17mEq/L, respectively.

A PEG tube was eventually placed as his inability to meet his nutritional needs remained a challenge due to oropharyngeal dysphagia. He was started on *S. boulardii* probiotics within 24 hours of the PEG tube placement. We diagnosed the patient with invasive *Saccharomyces cerevisiae* fungemia with concomitant vancomycin-resistant *Enterococcus faecium* (VRE) septicemia three days after starting the probiotics. We also diagnosed him with polymicrobial peritonitis because his ascitic fluid analysis isolated *Saccharomyces cerevisiae* and *Streptococcus oralis* (*S. oralis*).

We believe that the patient developed *Saccharomyces cerevisiae* peritonitis from the placement of the PEG tube and the administration of *Saccharomyces boulardii* probiotics per the PEG tube. The context of ascites from his liver cirrhosis placed the patient at a much higher risk of peritonitis. The patient had his antimicrobials changed several times during his hospitalization. We empirically started him on fluconazole, then switched to micafungin and finally switched to liposomal amphotericin B for the treatment of invasive *Saccharomyces cerevisiae* fungemia and peritonitis. The patient received cefepime and vancomycin for culture-positive gram-positive cocci infection. He could not get gentamicin despite sensitivity results because of his developing acute renal failure with metabolic acidosis.

Table 3. Hospital course for the patient's third admission

Hospital Activities	Hospital Day	Comments/ Outcome
Completion of treatment for neurosyphilis	Hospital day 5	Patient still encephalopathic with poor insight and judgment
Blood culture	Hospital day 5	Blood culture reported as no growth
Liver ultrasound	Hospital day 5	Presence of free intraperitoneal fluid, cirrhosis and portal hypertension.
PEG tube placement	Hospital day 6	Indicated for enteral feeding due to inadequate nutritional intake and medications administration.
Start date of *S. boulardii* probiotics	Hospital day 7	*S. boulardii* probiotics was stopped on hospital day 29. *Patient was treated for 22 days.
Repeat blood Culture	Hospital day 10	On hospital day 18 2 organisms were isolated: 1. *S. cerevisiae* (sensitivity not routinely done at our hospital) 2.*Enterococcus faecium* -vancomycin-resistant (VRE) and penicillin-resistant but sensitive only to gentamicin.
Paracentesis (with the removal of 1500mls of ascitic fluid) and Ascitic Fluid Analysis	Hospital day 14	On hospital day 24 2 organisms were isolated in ascitic fluid aerobic culture: 1.*S. cerevisiae* (routine sensitivity testing was not done) 2. Streptococcus mitis / *S. oralis*
Discontinuation of steroid therapy	Hospital day 21	Due to fungemia despite concerns for adrenal insufficiency. *The patient received steroids for more than 2 weeks.
Blood Culture re collection date Culture	Hospital day 30	Blood culture reported as no growth *Documentation of eradication of bacteremia and fungemia.
Death Pronouncement	Hospital day 33	Diagnosis at death; multiple organ failure and shock.

With the new diagnosis of *Streptococcus oralis* peritonitis and worsening renal failure, we discontinued Cefepime and Vancomycin. Once antibiogram results returned we changed the patient's antibiotics to meropenem and linezolid for the treatment of both VRE bacteremia and *S. oralis* peritonitis. The patient developed multiple organ failure with acute hypoxemic respiratory distress, and hypotensive shock. The patient died in our intensive care unit 12 days after stopping his steroids. Table 3 summarizes the patient's third hospital course.

4. Discussion

Clinical presentation

The spectrum of clinical presentation of emerging invasive *S. cerevisiae* infection is still evolving. Often the associated symptoms and clinical signs of the infection are usually nonspecific and may mimic the symptoms and signs of patients' comorbid diseases. *Saccharomyces cerevisiae* fungemia; defined as the isolation of the fungus in blood, is the most common clinical entity associated with invasive *Saccharomyces cerevisiae* infection. Other clinical entities related to invasive *S. cerevisiae* infection include; endocarditis, pneumonia, liver abscess, chorioretinitis, esophageal ulcer, esophagitis, unexplained fever, and septic shock [4,5,6].

A link between Crohn's disease and *S. cerevisiae* exists. The presence of antibodies against *S. cerevisiae* is used in its diagnosis [28]. Cases of *S. cerevisiae* peritonitis have been reported [29,30]. However, *S. cerevisiae* peritonitis resulting from the combination of a new PEG tube placement and PEG tube administration of *S. boulardii* probiotics in a patient with ascites was not found in the literature. Our patient developed invasive *S. cerevisiae* within the first three days of his exposure to *S. boulardii* probiotics. A systematic review article demonstrated that the duration of time from exposure of Saccharomyces probiotics and the development of fungemia is variable, ranging from one day to more than one month [5].

Pathophysiology

The pathogenesis of the invasiveness of *S. cerevisiae* seems elusive. One may speculate that the isolation of this seemingly non-pathogenic organism in sterile sites and body fluids is indicative of its ability to breakdown or disrupt intact intercellular junctions and cellular matrix contacts; a crucial structural component for the formation and maintenance of epithelial barrier against human commensals and invading organisms. We think the disruption of intact epithelial mucosal barriers creates the portal of entry for host cell invasion, migration and the dissemination of the fungus into naturally sterile sites and eventually into the bloodstream. This pathophysiologic process is called transmigration and has been described in the pathogenesis of *Campylobacter jejuni*. The transmigration of *Campylobacter jejuni* after the consumption of contaminated foods can cause mild bacterial gastroenteritis to severe diseases like reactive arthritis or Guillain-Barre Syndrome in humans [31].

We believe that our patient developed invasive *S. cerevisiae* infection from the "physical disruption" in his gastrointestinal tract mucosa barrier through the insertion of a much needed PEG tube for his feeding, followed by the administration of *S. boulardii* for C. difficile colitis prophylaxis through the PEG tube. Retrospectively, these two activities in the context of our patient who had multiple medical comorbidities, including ascites due to liver cirrhosis, led to the invasion and dissemination of *Saccharomyces cerevisiae* in him.

Occasional concomitant isolation of *S. cerevisiae* and a second microorganism has been documented [4,14]. The significance of the coinfection of *S. cerevisiae* with other organisms regarding the virulence of *S. cerevisiae* remains unclear. *S. cerevisiae* and *Enterococcus faecium* were isolated in the blood culture of our patient. Additionally, he had polymicrobial peritonitis with a coinfection of *S. cerevisiae* and Streptococcal oralis. *S. oralis* is an oral commensal in the Streptococcus mitis (S. mitis) family and a member of the Streptococcal viridian's group that occasionally causes opportunistic infections [32,33].

Diagnosis

The diagnosis of *S. cerevisiae* infection can be easily missed in the setting of a low index of clinical suspicion. Diagnosing invasive Saccharomyces infection can be challenging, since the isolation of *S. cerevisiae* in the setting of Saccharomyces colonization is nondiagnostic, especially when the associated clinical symptoms and signs are unremarkable. Hence, the need for a high diagnostic threshold for causation when the organism is isolated in sterile body sites or fluids, in patients treated with *S. boulardii* probiotics and patients not treated with Saccharomyces probiotics. Failure of a heightened index of clinical suspicion in high-risk hosts can result in a missed diagnosis or a delay in diagnosis with the likelihood of fatal outcomes.

Like many other rare invasive yeast pathogens, blood microscopy and culture are still the primary diagnostic tool in most clinical practices. The adoption of newer diagnostic tools may be necessary for prompt identification at the species level. While this approach seems promising, it is not yet routine and will still be dependent on the quality of the database employed. Furthermore, the lack of routine antimicrobial susceptibility testing for rare fungus contributes to missed opportunities in starting the appropriate antifungal therapy in a timely manner [34].

Treatment

The treatment of invasive *S. cerevisiae* infection is often based on expert opinion and in some cases, the provider's clinical experience. However, the joint ESCMID and ECMM clinical guidelines, [34], serves as a valuable resource for the curative treatment of invasive Saccharomyces infection. According to the joint guidelines, the strength of recommendation and quality of evidence for the Echinocandins is C-3. A grade C status implies marginal support of recommendation for use, while a level 3 quality of evidence implies that the evidence is from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees [34,35,36,37].

Based on the same guideline, the strength of recommendation and quality of evidence for amphotericin alone and amphotericin plus flucytosine is B-3, although both have a higher toxicity profile compared to the echinocandins. A grade B status implies that there is moderate support of recommendation for use, while a level 3 quality of evidence suggests that the evidence is from opinions of respected authorities. It is suggested that amphotericin plus flucytosine combination may be used in severe, or recurrent cases, or in cases where penetration into infected focus is challenging. The amphotericin and flucytosine combination reportedly have excellent in vitro susceptibility [34,39].

The strength of recommendation and quality of evidence for the fluconazole alone is D-3. A Grade D status connotes support of recommendation against the use, while a level 3 quality of evidence connotes that the evidence is from opinions of respected authorities. There is an increased occurrence of Saccharomyces fungemia and recurrent vulvovaginitis in patients exposed to fluconazole [4,34,35,40]. Although, the combination of IV amphotericin B and fluconazole appears to the most used pharmacologic regime [4].

It is assumed that the duration of treatment is the same as most antimicrobial syndromes, with a two-week course of therapy for fungemia, and up to 6 weeks or longer for seeding into other organs like osteomyelitis or when the endogenous etiology of fungemia remain unknown despite appropriate diagnostic workup [4,41]. The removal of central vascular catheters, and indwelling foreign bodies, as well as the discontinuation of probiotics, are strongly recommended. The strength of recommendation and quality of evidence for the discontinuation of probiotic in patients exposed to probiotics is A-3. A grade A status signifies strong support of the recommendation, while a level 3 quality of evidence connotes that the evidence is from opinions of respected authorities [4,5,34].

Prognosis

Invasive *S. cerevisiae* is a potentially fatal disease especially in at-risk patients with underlying medical diseases and associated predisposing factors, as exemplified in our patient and many other reported cases. Two research studies mentioned that the mortality rate associated with *S. cerevisiae* fungemia was about 15% and 30%, although these figures could not be totally due to fungemia alone [5,6]. Better outcomes and even cure are achievable by identifying the at-risk patient population, by clinical practice modification for the exclusion of high-risk patients from receiving *S. boulardii* probiotics, and by practicing stringent hand hygiene and proper environmental precautions. Early diagnosis and prompt initiation of proper management strategies are also critical.

Data on the morbidity rates associated with invasive Saccharomyces infection will be challenging to collate, as these patients often have multiple medical comorbidities that also affect their overall clinical outcomes. The diagnosis of adrenal insufficiency and invasive fungal infection in our patient poised a treatment dilemma for us. While continuing steroids in the setting of fungemia is contraindicated on the one hand, on the other hand, stopping steroids in the background of adrenal insufficiency can precipitate an adrenal crisis. We decided to stop our patient's steroids. It is still unclear to us if our patient's protracted illness and his eventual multiple organ failure and shock was due to adrenal crisis with the discontinuation of the steroids or due to the sequelae of invasive *S. cerevisiae* and its concomitant coinfections.

5. Conclusion

Continuous reporting of invasive *S. cerevisiae* infection could facilitate a better understanding of this clinical entity. We hope physicians and hospitals will evaluate their probiotics prescription patterns and define or redefine their exclusion criteria for the administration of probiotics. This evaluation of clinical practice can help reduce harm in our patients. Pending more extensive evidence, we would not recommend the concomitant administration of probiotics via a newly placed PEG tube particularly in patients at risk of peritonitis.

Lessons Learned

- Invasive *S. cerevisiae* is an emerging fungal infection. The infection has potentially fatal outcomes in hospitalized patients with multiple medical comorbidities and associated predisposing factors.
- We urge physicians to have a higher index of clinical suspicion for this rare and emerging infection in the right clinical setting. Prescribers of probiotics should especially be aware of this potential risk.
- Several associated factors affect the outcome of the infection. These include the risk of missed or delay in establishing the diagnosis, the vagueness of clinical symptoms which can mimic patients' underlying diseases, and the lack of awareness of standardized treatment.
- It is uncertain if co-infection with other organisms increases the virulence of *S. cerevisiae*.
- The consequences of *S. cerevisiae* nosocomial transmission in hospitalized patients can be massive. The initiatives for diligent hand hygiene by physicians and other hospital staff cannot be overstated.
- An important lesson we learned was that although this patient was compromised due to his underlying liver disease and ascites, the use of probiotics in a newly placed PEG tube should be used with caution in any patient until the newly created tract has had some time to seal post-placement.

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