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Saccharomyces cerevisiae fungemia: how heterogenous is their management?

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Abstract

Saccharomyces cerevisiae is a yeast used mainly as a probiotic for prevention or treatment of diarrhoea. However, the prevalence of *S. cerevisiae* fungemia has risen over the past years, notably among patients with predisposing factors. This retrospective study presents 21 cases of *S. cerevisiae* fungemia at the University Hospital of Liege from 2000 to 2022, their clinical relevance and therapeutic management. Each patient presented one or several risk factors prior to fungemia. The isolated strains presented high minimal inhibitory concentration for fluconazole, while MICs for amphotericin B, voriconazole and echinocandins were low. Some patients received antifungal therapy, while for others only central and peripheral lines were removed and probiotics discontinued. The MICs obtained for voriconazole and echinocandins makes them an alternative treatment to fluconazole and amphotericin B as reported in other studies. Since a *S. cerevisiae* fungemia can induce the same complications as candidemia, follow-up blood cultures should be collected and metastatic foci should be looked for. This study showed an important discrepancy in the clinical management of infections due to *S. cerevisiae* and highlights the need for guidelines.

Keywords: *Saccharomyces cerevisiae*; yeast; fungemia; immunodeficiency; probiotics

Introduction

Since its discovery, *Saccharomyces cerevisiae,* commonly known as the baker's yeast, has been frequently used in the agri-food and medical sectors, quickly becoming an important microorganism offering plenty of possibilities in terms of nutrition and health. Its anaerobic facultative properties and its preference for aerobic fermentation even under fully aerobic conditions, known as the Crabtree effect, make it a basic element in the fabrication of bread, other baked goods, and in the production of alcoholic beverages and ethanol-based fuel[1,2]. The widespread use of the *S. cerevisiae* in these different sectors could be the reason it is found in the digestive and respiratory tract, vagina and skin of healthy individuals and is considered as an occasional commensal yeast[3,4]. In medicine, the main use of this yeast is as a probiotic. Indeed, its subtype, *S. cerevisiae var. boulardii*, is used as adjuvant in diarrheal diseases, including the prevention and treatment of infections due to toxigenic *Clostridioides difficile*[3,5–7]. As a consequence of the extensive use of this yeast in therapeutics, superficial and invasive infections induced by this yeast are increasingly reported in the general population, particularly in patients with risk factors and to a limited extent in immunocompromised patients (transplant patients and patients under immunosuppressive therapy). In 1980, Mary L. Eschete and her colleagues reported the first case of fungemia caused by *S. cerevisiae*, showing its opportunistic characteristics[8]. Since then, cases of invasive infections were reported all over the world, identifying *S. cerevisiae* as the 5th cause of fungemia[3,9–13]. In this retrospective study, we looked into the different cases of fungemia due to this yeast in the University Hospital of Liège, Belgium, between 2000 and 2022. We report here 21 cases of *S. cerevisiae* infections including their clinical relevance and therapeutic management. This study provided an opportunity to contribute to the understanding of this rare fungal disease and also discuss the

data and guidelines available in the current literature on the clinical relevance and therapeutic management of infections caused by *S. cerevisiae*.

Materials and methods

This retrospective study reports the cases of invasive infections due to *S. cerevisiae* that occurred from January 2000 to January 2022 at the University Hospital of Liège (Belgium), a tertiary center. Records of all positive blood cultures growing *S. cerevisiae* from patients hospitalized during this period, including those from the emergency unit, were collected. All clinical data were retrieved from laboratory records and medical files and retrospectively evaluated, including: age, sex, underlying conditions, the number of positive blood cultures per patient, the results of susceptibility testing, and the antifungal treatment. The predisposing factors were classified as such: broad-spectrum antibiotics (BSA), *S. cerevisiae*-based probiotics (SBP) intake, immunodepression, presence of central venous catheters and surgical procedure on the respiratory and digestive system, sites potentially colonized by *S. cerevisiae*. Patients' management, including antifungal treatment and non-therapeutic measures taken by the medical staff, such as the removal of central and peripheral lines and the discontinuation of probiotics intake, were registered. The outcome was considered favourable if the patient survived and the if infection was cured, as defined by negative blood cultures. Information concerning potential complications related to fungemia was not included because it was not always documented in the medical records.

All blood culture samples were collected in pairs, aerobic and anaerobic, using FAN® Plus bottle (bioMérieux, France). The positivity was determined by reflectometry in the BACT/ALERT® 3D (bioMérieux, France) and the yeast was identified using the MALDI-TOF Mass spectrometry (Bruker Daltonics, Germany). The antifungal susceptibility testing was performed by microdilution using the Sensititre™YeastOne™ YO10 AST Plate (ThermoFisher

Scientific, USA) and with the antibiotic gradient method ETEST® (bioMérieux, France). The interpretation of minimal inhibitory concentrations (MICs) values was done in both cases using CLSI M60 guidelines for *Candida* species.

The protocol for this study was submitted to the University of Liège's Hospital and Faculty Ethics Committee (2023/150), which, given the purely retrospective nature of the study, considered that it did not fall within the scope of the law of March 7, 2004 relating to experiments on the human person, and therefore issued a favourable opinion.

Results

During the study period, 21 cases of *S. cerevisiae*-induced fungemia were diagnosed, with the first one occurring in 2016. A summary of all highlighted cases is presented in **Table A.1**. Mean age was 65.9 years and 14/21 (%) were female. All patients presented at least one predisposing factor, BSA intake being the most common (20/21, %), along with the presence of catheter lines (19/21, %) and immunosuppression (12/21, %). Ten patients out of 21 (%) were prescribed SBP prior or during their hospitalization. Five patients underwent an invasive surgical procedure on sites potentially colonized by *S. cerevisiae*: 2 total pharygolaryngectomy, a surgical treatment of Zenker diverticulum and the placement of a nasogastric feeding tube.

Antifungal susceptibility testing routinely included fluconazole and amphotericin B, while other antifungals were tested only on request. The strains isolated in this study presented minimum inhibitory concentrations (MICs) for fluconazole varying from 4 to >256 mg/L. When interpreted with the CLSI M60 guidelines for *Candida* species, *Candida glabrata* in particular, those MICs may be considered as sensitive at doses higher than the standard dosing amount (6mg/kg/day). The antifungal susceptibility testing also showed MICs ranging from <0.002 to 2 mg/L for amphotericin B. When interpreted with the CLSI M60 guidelines as well, those MICs may be considered as sensitive. As for voriconazole and echinocandins, they

presented MICs ranging from 0.064 to 0.25 mg/L and 0.25 to 2 mg/L respectively (**Table A.2**). In the CLSI M60 guidelines, there is currently no interpretation for the value obtained for voriconazole, however caspofungin may be interpreted as resistant in 3 cases out of 10 and anidulafungin in one case out of 6, according to the CLSI M60 guidelines for *Candida* species.

The majority of patients (15 out of 21) were treated with antifungals primarily. Five patients received fluconazole, 6 received caspofungin while the rest received amphotericin B (3/15) or voriconazole (1/15). Five patients were only treated by removing catheters and stopping probiotics. And last, one patient did not receive antifungals due to her critical state and palliative care was undertaken. Secondary exploration was performed for every patient (except for the latter patient) with follow up blood cultures (20/20), veinous Doppler (8/20) and fundus exam (8/20). One patient also underwent a transesophageal echocardiography, which turned out to be negative. Seven patients out of 15 were treated for 14 days after the first negative blood culture. The rest (8/15) received a shorter treatment depending on their clinical evolution, ranging from 3 to 11 days.

Regarding the non-therapeutic measures, the central and peripheral lines were removed for 14 out of 19 (%) and the intake of probiotic was stopped for 7 patients out of 10(%).

In terms of mortality, 5 of the 21 patients (%) reported in this case series study did not survive their hospitalization (**Table A.1**).

Discussion

Over the years, the number of superficial and invasive infections caused by *S. cerevisiae*, an apparently non-pathogenic yeast, has increased particularly in immunocompromised patients, to the point that it was upgraded from "Generally Recognized As Safe (GRAS)" to "Biosafety Level 1" status in Europe in 1996[14]. The EMA also published a document in 2017 warning against the use of Saccharomyces cerevisiae-containing probiotics in immunocompromised,

chronically ill patients or patients with a central venous catheter [15]. Although no strain specific analysis exists, safety of probiotics and particularly those containing *S. Boulardii* has been addressed in cases of fungemia involving critically ill and/or immune suppressed adult and pediatric patients [16-19]. Among the 92 cases of invasive infections documented in English, French, German and Spanish literature until 2005, only 17 were reported before 1990 and 76 after 1990[3]. Observed *S. cerevisiae* fungal infections were of varying severity: vaginitis, urinary tract infections, pulmonary infections, and fungemia[3,5,6,8,9,13,20–27].

S. cerevisiae is an opportunistic microorganism that takes advantage of weakened human defenses and intravascular devices to penetrate and spread inside the body. As shown in several studies, this yeast has the ability to withstand high temperatures, to proliferate and disseminate in the form of spores. The examination of different strains showed that *S. cerevisiae* is capable of growth at temperatures between 37 and 40°C, the most virulent ones until 42°C[14]. Furthermore, some strains can grow pseudohyphae and produce phospholipases and proteinases, which are major virulence factors[14]. They are also able to induce the release of proinflammatory cytokines from macrophages, causing an inadequate response by overstimulating the immune system[14,28–31]. R. Perez-Torrado *et al.* showed that *S. cerevisiae* strains, isolated from dietary complement, can survive phagocytosis[28]. Those strains are variant in the transcript factor Yap1p that is involved in oxidative stress response and can resist the effects of reactive oxygen species (ROS) produced by the macrophage[28].

The increase in *S. cerevisiae*-induced infections, particularly fungemia, is targeting patients with risk factors. BSA intake and the presence of peripheral catheter lines are the most common predisposing factors reported in the literature. Moreover, treatment with probiotics containing *S. cerevisiae var. boulardii* or immunodepression are also risk factors for bloodstream infection[3,6,8–10,12,14,20,26,32].

The sources of infection are diverse: they may be endogenous through respiratory or gastrointestinal translocation in patients colonized with *S. cerevisiae*, or exogenous for example from the hands of healthcare workers who have handled probiotics or by the presence of yeasts on surfaces such as catheters and peripheral lines[3,13].

The 21 presented cases are in line with the recent literature: *S. cerevisiae* fungemia appeared recently and patients had a predisposing condition. The lack of cases detected between 2000 and 2016 could be attributed to, among other things, the evolution of diagnostic methods and the increase of immunocompromised patients or intensification of immunosuppressive regimens. In our series, all patients that had a positive blood culture with *S. cerevisiae* presented at least one predisposing factor among which: BSA administration, presence of central venous catheters, long-term corticosteroid therapy or chemo- or radiotherapy in oncologic patients. The use of SBP and BSA in immunocompromised patients favored/facilitated the development of a systemic fungal disease.

Once the diagnosis is made, the challenge lies in the therapeutic approach. Wild-type strains of *S. cerevisiae* are able to grow slowly in synthetic environment, lacking amino-acids and other precursors but clinical strains tend to grow poorly. Consequently, it can take a few days to have a significant culture growth to allow the *in vitro* susceptibility testing and more than 24 hours (up to 72h) to recover the MICs. Moreover, in terms of antifungal susceptibility testing, there are no available clinical breakpoints for the interpretation of *S. cerevisiae* MICs. Nevertheless, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published in 2014 a report regarding the management of rare invasive yeast infections in which they highlighted the similar susceptibility pattern between *S. cerevisiae* and *Candida glabrata* (with higher MICs to azoles and lower MICs to amphotericin B) and the need, in severe cases, for a systemic antifungal treatment combined with discontinuation of probiotic intake and the

removal, when possible, of foreign devices[12]. Some review articles considering several reported cases of fungemia with *S. cerevisiae* showed a certain resistance to fluconazole with higher MICs in the *S. cerevisiae* strains isolated[3,12,14] whereas amphotericin B demonstrated lower MICs[3,12]. The same review articles also reported lower MICs for voriconazole than fluconazole and more successful outcomes with this azole[3,14].

In the cases diagnosed at the University Hospital of Liège, antifungal susceptibility testing routinely included fluconazole and amphotericin B, while other antifungals were tested only on request. High MICs were recorded for fluconazole, in accordance with the literature, which may indicate a lower efficacy for this azole *in vivo*. When tested, the antifungal susceptibility testing results for voriconazole, caspofungin and anidulafungin showed a good susceptibility profile with low MICs. They, therefore, represent a good alternative to liposomal amphotericin B or fluconazole and we believe they should systematically be included in the panel of antifungals tested. This would also provide more robust epidemiological resistance data for this yeast.

In an article published in 2021, the European Confederation of Medical Mycology (ECMM), in collaboration with the International Society for Human & Animal Mycology (ISHAM) and American Society of Microbiology (ASM), a panel of experts whose intention was to propose an update to the 2014 ESCMID recommendations, recommended for the systemic antifungal treatment of *S. cerevisiae* fungemia, the use of amphotericin B as first-line therapy and fluconazole or echinocandin as first-line alternative[33]. The reviews and case reports published in the literature also provide useful guidance for the management of these infections. Some reports show that when treated with antifungals, the outcome of *S. cerevisiae*-induced fungemia is more often favorable with amphotericin B (77.7% of recovery) than with fluconazole (60%) [3,12]. However, due to the adverse effects associated with the amphotericin B treatment, such as nephro- and hematologic toxicity, its use is limited particularly in fragile

patients[14]. Voriconazole, and echinocandins demonstrated a good susceptibility profile with low MICs and favorable clinical and biological responses[3,12,14].

In our case-series, 15 patients out of 21 received an antifungal treatment. Despite the susceptibility testing results favorable to the use of amphotericin B, its adverse effects and the lack of guidelines in the clinical management of *S. cerevisiae*-induced fungemia are probably the reason why fluconazole and caspofungin were the treatments mainly chosen by clinicians. Given the *in vitro* susceptibility profile of *S. cerevisiae*, we believe that the same recommendations as the recent guidelines for the management of non-candida yeast invasive infection could be applied for the treatment of *S. cerevisiae* fungemia: the use of amphotericin B as first-line therapy and fluconazole or echinocandins, as first-line alternative. However, the correct dosage for each antifungal still needs to be determined, especially for fluconazole.

We also observed that, despite the dosage of each antifungal was similar between patients, the duration of treatment was very different depending on the case. It would therefore be necessary to standardize the therapy duration and in the lack of guidelines and by analogy to the therapy duration applied for *candidemia*, patients with *S. cerevisiae* fungemia which clinical status requires antifungal treatment, could be treated for 14 days after the first negative blood culture. Furthermore, since an infection with this yeast can clinically be equivalent to invasive candidiasis, follow-up blood cultures must be drawn and a secondary location of infection must be sought. The risk of complications, such as septic emboli and suppurative thrombophlebitis (when a catheter is involved), should also be assessed by performing a fundoscopic examination and a venous Doppler[34,35]. In our population, each patient had follow-up blood cultures but only 8 out of 21 had a Doppler and a fundus. This inconsistency in the management of this rare fungemia can be attributed to the lack of guidelines for treatment, follow-up and search for other infection sites.

Nevertheless, the use of antifungals is not the only way to treat infections caused by *S. cerevisiae* and is not always necessary. In order to achieve the most favorable outcome, multiple measures need to be taken such as the removal of all central venous catheters and the interruption of probiotics intake[3,5,6,8,9,12,14,20,23,24,26,27]. In our series, 5 patients had a favorable evolution without antifungals, only after removing the catheters and stopping the SBP.

As many studies show, this infection although invasive, does not appear to be fatal and the survival rate in our study population was 76% with deaths not directly attributable to the fungemia. Indeed, the patients who did not survive had very severe diseases and their death was deemed to be multifactorial.

Conclusion

Considering the results we observed and in accordance with the literature, *Saccharomyces cerevisiae*-based probiotics should be use with prudence as they are implicated in 47.7% of the infections presented and it is necessary to limit the contact of immunosuppressed patients with these products. The use of appropriate antifungal therapy, removal of central venous catheters and discontinuation of the probiotics can result in a good clinical response and the patients' recovery in most cases. As well as with other yeast invasive infections, fungemia with *S. cerevisiae* needs a diagnostic evaluation to rule out metastatic foci and a follow-up including blood cultures. In terms of therapy, voriconazole and echinocandins may be a promising therapeutic alternative to fluconazole and amphotericin B. Besides, the initiation of an antifungal treatment does not always seem necessary and can be determined on a case-by-case basis, depending on the patient's clinical status.

The major issue with *S. cerevisiae*-induced fungemia is the lack of clinical breakpoints for the interpretation of antifungal susceptibility testing to guide treatment and follow-up

investigations. Therefore, it is crucial to improve the global management of *Saccharomyces*-induced fungemia.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contribution's statement

Coumba Diop and Marie-Pierre Hayette conceived the original idea.

Coumba Diop collected the data and wrote the manuscript with support from Julie Descy.

Rosalie Sacheli, Cécile Meex, Nathalie Layios and Marie-Pierre Hayette contributed to the final version of the manuscript.

Marie-Pierre Hayette supervised the project.

All authors provided critical feedback and helped shape the research, analysis and manuscript.

Appendices

Patient	Age	Sex	Underlying condition	Peripheral lines	Probiotic use	Previous antimicrobial therapy	Number of positive blood cultures	Treatment	Outcome
1	89	F	Severe septic shock on a urinary infection Dyspnea and metabolic acidosis	Yes	Yes	Ceftriaxone Clarithromycin Amikacin	1	Palliative care	Deceased during fungemia
2	66	F	Metastatic lung adenocarcinoma treated with immunotherapy Dyspnea and general asthenia	No	No	Piperacillin-Tazobactam	3	Amphotericin B: 5mg/kg/24h during 14 days Replacement of the central and peripheral lines	Deceased during fungemia
3	50	M	Hypopharyngeal neoplasia treated with radio- and chemotherapy Nasogastric tube feeding	Yes	Yes	No	1	Fluconazole: 400mg/24h during 4 weeks Catheter removal Stopping probiotic intake	Survived
4	77	F	Aortic valve replacement complicated by a bronchopneumonia	Yes	Yes	Ceftazidime	1	Fluconazole: 400mg/12h during 5 days Replacement of the central and peripheral lines Stopping probiotic intake	Survived
5	74	M	Metastatic pulmonary adenocarcinoma treated with immune- and radiotherapy Bronchopneumonia	Yes	No	Piperacillin-Tazobactam	5	Fluconazole: 400mg/24h during 8 days	Deceased after fungemia

6	73	F	Methicillin-susceptible staphylococcus aureus mediastinitis after an aortic valve replacement and a double coronary bypass	No	Yes	Piperacillin-Tazobactam Flucloxacillin	1	Caspofungin: 50mg/24h during 3 days Stopping probiotic intake	Survived
7	82	F	Paroxysmal atrial fibrillation Acute pulmonary embolism with a pulmonary infection Bacteremia	Yes	No	Meropenem	1	Caspofungin: 50mg/day during 10 days Central and peripheral catheters removal	Deceased during fungemia
8	83	F	Hip prosthesis infection Pyrexia and an important inflammatory syndrome	Yes	Yes	Flucloxacillin Rifampicin Moxifloxacin	1	Catheter withdrawal Stopping probiotic intake	Survived
9	54	F	Esophageal carcinoma Total pharyngolaryngectomy with an ileocolonic reconstruction	Yes	Yes	Meropenem	9	Amphotericin B: 5mg/kg/24h up to 14 days after the first negative BC Stopping probiotic intake	Survived
10	85	F	Pulmonary infection Respiratory decompensation	Yes	No	Piperacillin-Tazobactam Clarithromycin Cefepime	1	Catheter removal	Survived
11	70	F	Supra-ventricular arrythmia Sepsis from a pulmonary infection	Yes	No	Meropenem Ciprofloxacin	1	Fluconazole: 400mg/12h during 6 days Palliative care	Deceased during fungemia
12	66	M	Epidermoid carcinoma of the hypopharynx	Yes	No	Piperacillin-Tazobactam	4	Amphotericin B: 5mg/kg/24h up to 14 days after the first negative BC	Survived

			Total circular pharyngo-laryngectomy Dyspnea and infection at the tracheostomy site						
13	41	M	Acute myeloid leukemia Aplasia Bacteriemia	Yes	No	Meropenem Cefepim Vancomycin Amikacin	1	Caspofungin: 50mg/day during 11 days Catheter removal	Survived
14	60	M	Road accident: polytrauma and aortic dissection	Yes	No	Piperacillin-Tazobactam Meropenem	1	Caspofungin: 50mg/day up to 14 days after the first negative BC Catheter removal	Survived
15	32	F	Diabetic acidosis Covid 19 pneumonia	Yes	No	Amoxicillin-Clavulanic acid Piperacillin-Tazobactam Clarithromycin	1	Catheter removal	Survived
16	77	F	Covid 19 pneumonia	Yes	Yes	Amoxicillin-Clavulanic acid Doxycycline	1	Catheter removal	Survived
17	66	F	Zenker surgery complicated by fistulization and mediastinitis	Yes	Yes	Amoxicillin-Clavulanic acid Cefotaxim	2	Caspofungin: 50mg/day up to 14 days after the first negative BC Catheter removal	Survived
18	43	F	Bacteriemia	Yes	No	Piperacillin-Tazobactam Ciprofloxacin	1	Fluconazole: 400mg/12h up to 14 days after the first negative BC Catheter removal	Survived
19	90	M	Bibasal bronchopneumonia on severe dysphagia	Yes	No	Cefepim Minocycline	1	Catheter removal Stopping probiotic intake	Survived

						Meropenem Vancomycin			
20	44	F	Bilateral pneumonia	Yes	Yes	Amoxicillin-Clavulanic acid	1	Caspofungin: 50mg/day up to 14 days after the first negative BC Catheter removal Stopping probiotic intake	Survived
21	63	M	Esophageal carcinoma Sepsis	Yes	Yes	Meropenem	1	Voriconazole: 200mg/12h during 2 days Catheter removal Stopping probiotic intake	Survived

Table A.1: Summary of 21 cases of *Saccharomyces cerevisiae*-induced fungemia

Patient	Antifungal susceptibility testing (mg/L)									
	Fluconazole		Voriconazole		Amphotericin B		Caspofungin		Anidulafungin	
1	Not realized									
2	96	R	0.064	ND†	0.19	S	2	R	/	
3	8	SDD*	/		<0.002	S	/		/	
4	8	SDD*	/		0.012	S	/		/	
5	8	SDD*	/		0.004	S	/		/	
6	12	SDD*	/		0.008	S	0.5	R	0.5	R
7	4	SDD*	0.064	ND†	0.125	S	0.25	I	/	
8	4	SDD*	0.094	ND†	0.08	S	/		/	
9	12	SDD*	/		1	S	/		/	
10	>256	R	/		2	S	/		/	
11	16	SDD*	0.25	ND†	2	S	/		/	
12	8	SDD*	/		<0.002	S	/		/	
13	16	SDD*	0.004	ND†	0.75	S	0.032	S	/	
14	1	SDD*	/		0.25	S	0.75	R	0.38	I
15	24	SDD*	/		0.75	S	0.125	S	0.094	S
16	16	SDD*	/		0.75	S	0.125	S	0.032	S
17	4	SDD*	0.12	ND†	0.25	S	0.25	I	0.12	S
18	0.5	SDD*	≤0.008	ND†	0.5	S	0.06	S	0.03	S
19	16	SDD*	0.125	ND†	1	S	/		/	
20	Inconclusive									
21	0.5	SDD*	0.015	ND†	0.25	S	0.03	S	/	

Table A.2: Antifungal susceptibility testing for each strain isolated

*SDD = Susceptibility depends on achieving the maximum possible blood level

†ND= Not determined

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We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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