

Rare Yeasts: Emerging Threat in Immunocompromised Patients

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ABSTRACT

Fungemia due to the yeasts other than *Candida* is a clinically rare, but still emerging entity. The clinical terminologies of *rare opportunistic yeast bloodstream infections* (ROYBSIs) or *micafungin breakthrough fungemia* (MBF) or *echinocandin non-susceptible yeast* (ENSY) refer mostly to the same entity. Clinicians should be alert about the early distinction. ROYBSIs are mostly resistant to echinocandins and should be taken into consideration when yeast growth in blood culture of a patient previously treated with an antifungal, especially an echinocandin. Apart from molecular methods, MALDI-TOF might be considered as the most useful commercial system for identification of ROYBSIs. A combination of L-AmB and voriconazole is the appropriate empirical therapy for MBF, especially in neutropenic patients.

Keywords: Candidemia, Non-*Candida*, yeast, fungemia, echinocandin resistant, breakthrough, non-susceptible, bloodstream

INTRODUCTION

Infections of the yeasts other than *Candida* spp. are rare, but an emerging clinical entity. Clinicians should be alert for early diagnosis. Early distinction of non-*Candida* yeasts is important because of varying antifungal susceptibilities, higher mortality of 50-80% particularly among immunocompromised patients (1). These yeasts include Basidiomycetes (*Cryptococcus*, *Trichosporon*, *Rhodotorula*, and *Malassezia* species) and the non-*Candida* Ascomycetes (such as *Hansenula*, *Saccharomyces*, *Saprochaete capitata*, and *Saprochaete clavata*). Basidiomycetes are less susceptible to all antifungal drugs compared to Ascomycetes due to the difference in their cell wall integrity (2). *Cryptococcus*, *Trichosporon*, *Rhodotorula*, and *Saccharomyces* species are intrinsically resistant to echinocandins, and *Trichosporon* species could also be resistant to amphotericin (3). Moulds such as *Fusarium* spp., *Scedosporium* spp., or *Exophiala* spp. may cause to fungemia (4). These moulds and Cryptococci that was the leading second most common yeast after *Candida* spp., were not included in this review.

Several non-*Candida* yeasts were reported to be resistant to echinocandins, as a distinction to *Candida* spp. infections. The terminologies of *rare opportunistic yeast bloodstream infections* (ROYBSIs) or *micafungin breakthrough fungemia* (MBF) or *echinocandin non-susceptible yeast* (ENSY) were used (2, 5, 6).

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We present three cases of rare yeast fungemia and review the rare yeast infections with emphasis on diagnostic and therapeutic approach.

Case 1. *Saprochaete capitata* fungemia

A 73-year-old male with a history of myelodysplastic syndrome for nine years, who had a lower extremity amputation due to peripheral artery occlusion, and recurrent urosepsis with chronic renal failure was admitted to intensive care unit (ICU). After a successful resuscitation following cardiac arrest 20 days ago, he had been ventilated via tracheostomy and had tunnelled central venous catheter (CVC) for three months. While he had given micafungin for severe neutropenic fever with candiduria, *S. capitata* was isolated in his blood culture. His catheters were removed, and voriconazole was started. No fungus was recovered in his next cultures. After 14 days he died with septic shock due to an episode of *P. aeruginosa* bacteremia.

Case 2. *Saprochaete clavata* fungemia

A 21 years-old female with early recurrence of acute myeloid leukaemia after allogeneic stem cell transplantation, had several febrile neutropenia episodes. On the 30th day of micafungin therapy, *S. clavata* was detected in her blood culture. Both amphotericin B and voriconazole were given, and central catheters were removed. No pathogen was detected in her blood cultures after ten days of treatment, but she died because of the intracranial haemorrhage three weeks later. To our knowledge, this was the first reported case of *S. clavata* fungemia in Turkey as a pathogen of MBF.

Case 3. *Kodamaea ohmeri* fungemia

A 43-year-old female, who was operated for colon tumour and had splenectomy in 2016, and received chemotherapy. Following removal of multiple nodules in the lung, the yeast-like fungus was reported in the blood culture. Micafungin was started, and CVC was removed. Pathology revealed nodular necrotizing granulomatous inflammation with oval or spherical, different sized fungi. *K. ohmeri* was clarified as the agent by VITEK2YST card (Biomerieux®) and MALDI-TOF. She was treated for four weeks of intravenous fluconazole with cure.

The incidence of Non-*Candida* yeasts

The incidence of non-*Candida* and non-*Cryptococcus* yeasts in blood cultures was reported to be lower than candidemia. In a study, ROYBSIs were isolated from 94 blood culture specimens out of 41 patients, representing 0.18% of all positive blood cultures, 2.8% of all positive fungal blood cultures and 3.1% (94/2984) of all positive blood culture for yeasts, so that the incidence of ROYBSIs was reported as 2.1 cases/100,000 patient-days (6). The incidence of ROYBSIs varied from 1.0% to 34% according to different countries, patient populations and medical settings. In a one-year surveillance study conducted in 25 hospitals across Asia, ENSY accounted for 6.7% of 2155 non-duplicate isolates from the blood (2).

The proportions of individual species (*Cryptococcus*, *Trichosporon* and *Rhodotorula*) vary according to the sample size of the studies or variations between countries. In reports from Belgium and Denmark, *Saccharomyces cerevisiae* was the predominant non-*Candida* isolate, while *Trichosporon* species in Asian countries, and *Rhodotorula* in a US single centre, Spain, and ARTEMIS study (2,7). A retrospective review of ROYBSIs between 1998 and 2010 in a cancer centre in Texas, USA, revealed *Rhodotorula* in 21 (51% of ROYBSIs) patients, *Trichosporon* in 8 (20%) patients, *S. cerevisiae* in 8 (20%) patients, *Geotrichum* in 2 (5%) patients, *Pichia anomala*, and *Malassezia furfur* in one patient each (6).

The survey from a large (1900-bed) university hospital in Belgium reported incidence of fungemia and the distribution of species. They found that the annual incidence of fungemia ranged between

HIGHLIGHTS

- The yeasts other than *Candida* is emerging and clinicians should be alert about early distinction.
- MALDI-TOF might be considered as the most useful commercial system for identification
- A combination of L-AmB and voriconazole is the appropriate empirical therapy for especially in neutropenic patients.

1.30 and 1.68 episodes per 10 000 patient-days (on a total of 2 680 932 patient-days). *S. cerevisiae* was reported 0.7% (3/427 fungemia isolates) during this 2001-2005 period (8). Since only germ tube production and chromogenic media supplemented with API ID 32 were used with no available MALDI-TOF, no other yeast seems to be recognized in this survey.

Non-*Candida* fungemia was reported mostly as breakthrough infections, between 49% (20/41 fungemia) and 59% (10/17 cases) among fungemia studies (6, 9). This ratio was about 20% (52/258 cases) for *Candida* fungemia in cancer patients from European Organization for Research and Treatment of Cancer (EORTC) centres (9). Non-*Candida* fungemia had higher mortality than *Candidemia* (54.5% versus 21.2%, $P = 0.03$) in a study of 110 episodes of fungemia with clinical sepsis from Kyoto, Japan, with the leading agents of *C. neoformans* and *T. asahii* (3).

Risk factors

Prior colonisation seems to be an important predictor of non-*Candida* fungemia. A study from Japan aimed to compare the non-*Candida* fungemia and candidemia in a tertiary hospital between 2004 and 2009, and the presence of collagen disease [odds ratio (OR) 9; 95% confidence interval (CI) 1.58-51.4; $p=0.01$] or renal replacement therapy (OR 15; 95% CI 3.06-73.4; $P < 0.01$) were found to be significantly more common in non-*Candida* fungemia group (3). While presence of solid malignancy was a risk factor for candidemia (0% vs 45%, $p<0.01$), prior bacteremia was found to be a risk factor for non-candidemia attacks (63.6% vs 32.3%, $p= 0.04$). The presence of catheter was found in 51% of the patients with ROYBSIs, most of whom had solid or haematological malignancy (6).

How to differentiate *Candida* from other yeasts in positive blood cultures?

If *Cryptococcus* is suspected, urea test and inoculation in Niger culture medium should be applied (10-12). All *Trichosporon* isolates might be named in species level based on urease production and the presence of arthroconidia (10). Commercial systems, such as the Vitek Yeast Biochemical Card, API 20C, and API ID32C (bioMérieux®) need an incubation period of 24 to 48 h, and their application is mostly limited because of small databases (13).

The *C. albicans* germ tube antibody (CAGTA) test consists of an immunofluorescence assay to detect antibodies against an antigen of *C. albicans*, hwp1. Besides *C. albicans*, other *Candida* species are able to produce hwp1 to some degree. Whenever *Candida* hyphae invade body tissues, a positive serum CAGTA is supposed to be detected. Jimenez et al. reported that candidemia with a positive CAGTA should be considered as invasive candidiasis (14).

The combinations of CAGTA and (1-3)-b-D-glucan (BDG) or CAGTA and mannan antigens (Mn) had high NPV at the alternative cut-offs and could be useful in discontinuation of unnecessary empirical therapy in patients with suspected candidemia (15). The recommendations by European Conference on Infections in Leukemia (ECIL) for the biomarkers in diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients were at the moderate level for BDG detection in serum (BII), and the combined Mn/Anti-Mn testing in serum for hepatosplenic candidiasis (B III), and candidemia (C II). No recommendations were formulated for the use of PCR owing to a lack of standardization and clinical validation (16). According to the guideline of European Society of Clinical Microbiology and Infectious Diseases (ESCMID) the serum Mn/Anti-Mn was recommended for the diagnosis of candidemia but not for diagnosis of invasive candidiasis, and BDG was recommended to rule out *Candida* infection (12). On the other hand, findings suggest a possible role for BDG testing in diagnosis, and also treatment response of *S. clavata* infections (17).

With a protocol lasting 4 hours, rapid identification of *Candida* species from positive blood cultures by combining PCR and pyrosequencing of a small region of the 18 S rRNA gene is also proposed (18).

An oligonucleotide array system targeting the internal transcribed spacer (ITS) for rRNA genes was used to analyse 116 fungus-positive blood cultures from 105 patients, and high specificity and sensitivity were obtained compared to traditional methods (19). In a study by Hsiue et al., an array was developed to identify 77 species (16 genera) of medically relevant yeasts, including *Cryptococcus*, *Rhodotorula*, *Saccharomyces*, and *Trichosporon* species within 16-24 hours, and the sensitivity of 100% and the speci-

ficity of 97% were obtained (20). MALDI-TOF was gradually implemented, and now is the backbone for the final identification. MALDI-TOF MS protocol was reported to be able to identify *Fusarium*, *Exophiala*, *Saprochaete*, and *Trichosporon* species directly from aliquots of positive BCs (20).

T2 magnetic resonance using nanoparticles has been approved for clinical usage (T2 *Candida*, T2 Biosystems, USA). The assay detects *Candida* species (*C. albicans*/*C. tropicalis*, *C. parapsilosis*, and *C. krusei*/*C. glabrata*) directly from positive blood samples, but not differentiate viable organisms. It also seems helpful for patients with candidemia under therapy. It has a sensitivity of 91 % with a time to positivity of 4.4 hrs and a limit of detection of 1–3 CFU/mL (21).

Trichosporon sp.

Trichosporon infection has a high mortality rate (53%–76%) and could be misdiagnosed as *Candida* infection (1). The cryptococcal latex test might result with false-positivity in patients with disseminated *Trichosporon* infection due to shared antigens (22). *Trichosporon* is the second most common yeast among the patients with fungemia in haematological patients and frequently the pathogen of breakthrough invasive fungal infection (bIFI) in patients receiving antifungal therapy. *Trichosporon* fungemia was significantly correlated with neutropenia than other ROYBSIs. Seven strains from 39 patients with haematological diseases with MBF between 2008–2015 were reported to be *Trichosporon asahii* (5).

In a review of 185 cases of *Trichosporon* fungemia, the number of cases increased from 1975 to 2014, especially over the past decade (1). The review revealed that a negative outcome was associated with a history of antimicrobial use, bacterial bloodstream co-infection, prophylactic/empirical antifungal therapy, *Trichosporon beigeli* infection, and receiving the antifungal regimen of amphotericin B/liposomal amphotericin B. A significantly greater proportion of patients with a positive outcome had fungemia without invasive tissue infection and received a voriconazole regimen or an amphotericin-triazole combined regimen. The significant positive outcome was also reported with patients who had recovered from neutropenia or after CVC removal (1).

Saprochaete capitata (Bastoschomyces capitatus)

Saprochaete spp. are filamentous fungi. In culture, dry, cottony colonies consisting of hyphae with arthroconidia were observed (23), which differs from the colonies of *Candida* spp. They were previously considered to be non-pathogenic. In microscope, the isolates produce hyphae, pseudohyphae, blastoconidia, arthroconidia and annelloconidia (24). *Saprochaete* spp. may colonize skin and mucosae and cause to infections in patients with underlying hematologic malignancies (25). In report from Spain, 20 out of 25 acute leukemia patients had fungemia with visceral dissemination with 30-day mortality of 52% (26). In a report from Turkey, from 2012 to 2015, a total of 20 *S. capitata* strains were isolated from onco-haematological and ICU patients in a university hospital (27). It was involved with many outbreaks and contaminated dairy products (25). Spondylodiscitis in a patient with solid organ tumour, fungemia in a non-neutropenic patient after aortic valve replacement, and opportunistic infections in polymyositis and dermatomyositis patients were also reported (28–30).

Saprochaete clavata

Saprochaete clavata (*Geotrichum clavatum*) is a rare, but still emerging yeast. It was thought to be frequently mistaken for *G. capitatum* and *G. candidus* on account of erroneous and limited databases of automated systems (25, 31). *S. clavata* was more rarely isolated from human samples than *S. capitatum*. We summarized non-duplicate 56 cases of *S. clavata* infections reported in the literature (Table 1). A total of 37 of the patients had AML, and the fatality rate was 66% (Table 1).

In France, they represented 2.5% of the 8366 invasive yeast isolates in a prospective surveillance programme from 2002 to 2018, CNRMA. In this study, *Saprochaete* spp. was placed after *Cryptococcus* (14.5%), and before *Saccharomyces* (0.7%), *Trichosporon* spp. (0.6%), *Rhodotorula* (0.5 %) (31).

S. clavata had been rarely reported in monocentric outbreaks in Europe until 2012. Then a multicentric outbreak in haematology wards in France, with 33 cases of *S. clavata* invasive infections was reported. Seventeen cases of them were diagnosed within two months period in three health care fa-

Table 1. The cases infected with *S.clavata*, including our cases (references, 17, 23,32, 33, 39-47).

Study	n	Sex (M/F)	Cyta Rabine exposure	Diagnosis	Prophylaxis	Culture result	Infection site	Empirical therapy	Directed therapy	Outcome
Vaux et al.	30	15/15	18/23	21 AML 6 ALL	-	Blood, Respiratory	BSI, Pneumonia	Caspo (16 cases)	-	24/30 died
Picard et al.	3	2/1	3/3	3 AML	Posa	Blood	Lung, intestine, cardiac	Caspo	L-amb and vori	3/3 died
Camus et al.	1	1/0	1/1	1 AML	Posa	Blood	Liver, peritoneum	Caspo	Vori	Alive
Lacroix et al	2	2/0	2/2	2 AML	No	Blood, urine, skin		Ampho	L-amb and vori with flusitozin	Alive
Favre et al.	1	1/0		Aplastic anaemia	No	Blood, stool	Liver, spleen, lung, kidney, bowel	Caspo	L-Amb and vori	Alive
Del Principe et al.	3	1/2	3/3	2 AML 1 NHL	Posa	Blood	Lung, spleen, liver	-	L-Amb (high dose) with oral vori	Alive
Fernández et al.	1	1/0		1 Lymphoma	-	Blood	Blood, skin	-	L-Amb	died
Buchta et al.	6	1/6	6/6	5 AML, 1 Lymphoma	-	Blood Stool, wound, bile, urine	Blood Disseminated, Res	-	Vori/ LC-Amb/D- Amb	5/6 died
Liu et al.	1	1/0	0/1	ALL	Micafungin	Blood, hepatic	Blood, abdomen	Vori	L-Amb	Alive
Leoni et al.	1	1/0	0/1	HSCT	Low dosage L-Amb	Blood	Blood, skin, pulmonary	Vori/L-Amb	Vori/L-Amb	Alive
Stanzani et al.	4	3/1	1/4	2 AML, 2 NHL	Micafungin, Anidulafungin	Blood, BAL, Skin	Blood, lung, liver, spleen, CNS	Vori/L-Amb	Vori/L-Amb	¼ died
Wee et al.	1	0/1	0/1	ALL	-	Blood	Blood, skin	Vori/L-Amb	Vori/ L-Amb	Alive
Pavone et al.	1	0/1	0/1	Kidney transplant	Caspo	Blood	BSI	L-Amb	Vori/L-Amb	Died
Our case	1	0/1	1/1	AML	Micafungin	Blood	BSI	L-Amb	Vori/L-Amb	Died

BSI: bloodstream infection,
Caspo: caspofungin,

Vori: voriconazole,
L-Amb: liposomal amphotericin B,

D-Amb: Amphotericin- deoxycholate,
LC-Amb: lipid complex amphotericin



cilities, suggesting a common source of contamination (32), but not proven. In this outbreak, *S. clavata* was recovered mostly from the blood (37/41, 90%). The case fatality rate on day 60 was reported as 66%. The optimal therapy of invasive geotrichosis remains a challenge. Echinocandins are not recommended because of intrinsic resistance. Voriconazole, posaconazole (but not fluconazole), amphotericin B and 5-fluorocytosine are effective antifungal agents because of better *in vitro* and *in vivo* activities. Preventive antifungal posaconazole treatment, which seems to be effective in reducing the number of proven invasive fungal infections in haematological patients, did not prevent the development of this severe infection in some cases (23). This could be explained by subtherapeutic dosage due to gastrointestinal elimination of posaconazole suspension (23). A combination of amphotericin B with voriconazole could be better than voriconazole alone, but still remains undetermined (33). High-dose liposomal amphotericin B might be more effective than the standard dose.

Kodamea ohmeri

Kodamea ohmeri is from *Saccharomycetaceae* family, and was formerly known as *Pichia ohmeri*. It is an opportunistic pathogen among infants and older age groups with immunosuppression, hematologic malignancy or chronic lung disease with CVC source (34-36). *K. ohmeri* can present with different clinical features such as peritonitis, endocarditis, mediastinal mass, sepsis, oropharyngeal, and urinary tract infections (35,37). *Kodamea ohmeri* has a fermentation capability, therefore used in the

preparation of pickles (35). *K. ohmeri* had low MIC levels to all antifungal agents except fluconazole in few cases. *K. ohmeri* and *C. tropicalis* are similar phenotypically. In a pediatric centre, thirty-eight out of 148 (25.7%) phenotypically identified *C. tropicalis* isolates were confirmed as *K. ohmeri* by using advanced techniques. *K. ohmeri* has the potential to cause hospital outbreaks. Piperacillin-tazobactam use was reported to be significantly associated with the *K. ohmeri* fungaemia (38). Unlike the pathogens of ROYBSIs, *K. ohmeri* was reported to have low MICs to echinocandins. In our case 3, the *K.ohmeri* was susceptible to fluconazole, and the patient was cured with fluconazole.

CONCLUSION

Identification of the yeasts with conventional methods might be late, which may result with the inappropriate use of echinocandins in patients with ENSY fungemia. ROYBSIs should be taken into consideration when yeast growth in blood culture of a patient previously treated with an antifungal, especially an echinocandin. The slow growth of yeast in solid media, their colony type, and urease positivity might be helpful in the differentiation. Apart from molecular methods, MALDI-TOF might be considered as the most useful commercial system for identification of ROYBSIs. A combination of L-AmB and voriconazole might be the appropriate empirical therapy for MBF, especially in neutropenic patients. L-AmB might be reasonable for MBF in non-neutropenic patients.

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REFERENCES

- 1 Liao Y, Lu X, Yang S, Luo Y, Chen Q, Yang R. Epidemiology and outcome of *Trichosporon* fungemia: a review of 185 reported cases from 1975 to 2014. *Open Forum Infect Dis* 2015; 2: ofv141.
- 2 Lin SY, Lu PL, Tan BH, Chakrabarti A, Wu UI, Yang JH, et al. Asia Fungal Working Group (AFWG). The epidemiology of non-*Candida* yeast isolated from blood: The Asia Surveillance Study. *Mycoses* 2019; 62: 112-120.
- 3 Yamamoto M, Takakura S, Hotta G, Matsumura Y, Matsushima A, Nagao M, et al. Clinical characteristics and risk factors of non-*Candida* fungaemia. *BMC Infect Dis* 2013; 13: 247.
- 4 Paiva JA, Pereira JM, Tabah A, Mikstacki A, de Carvalho FB, Koulenti D, et al. Characteristics and risk factors for 28-day mortality of hospital acquired fungemias in ICUs: data from the EUROACT study. *Crit Care* 2016; 20: 53.
- 5 Kimura M, Araoka H, Yamamoto H, Nakamura S, Nagi M, Yamagoe S, et al. Micafungin breakthrough fungemia in patients with hematological disorders. *Antimicrob Agents Chemother* 2018; 62: e02183-17.
- 6 Chitasombat MN, Kofteridis DP, Jiang Y, Tarrand J, Lewis RE, Kontoyiannis DP. Rare opportunistic (non-*Candida*, non-*Cryptococcus*) yeast bloodstream infections in patients with cancer. *J Infect* 2011; 64: 68-75.
- 7 Marcos-Zambrano LJ, Escribano P, Sánchez C, Muñoz P, Bouza E, Guinea J. Antifungal resistance to fluconazole and echinocandins is not emerging in yeast isolates causing fungemia in a Spanish tertiary care center. *Antimicrob Agents Chemother* 2014; 58: 4565-72.
- 8 Lagrou K, Verhaegen J, Peetermans WE, De Rijdt T, Maertens J, Van Wijngaerden E. Fungemia at a tertiary care hospital: incidence, therapy, and distribution and antifungal susceptibility of causative species. *Eur J Clin Microbiol Infect Dis* 2007; 26: 541-7.
- 9 Cornely OA, Gachot B, Akan H, Bassetti M, Uzun O, Kibbler C, et al. Epidemiology and outcome of fungemia in a cancer Cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031). *Clin Infect Dis* 2015; 61 (3): 324-31.
- 10 A. M. Montoya, G. M. González *Trichosporon* spp: an emerging fungal pathogen. *Medicina Universitaria* 2014; 16(62): 37-43.
- 11 Chakrabarti A, Chatterjee SS, Rao KL, Zameer MM, Shivaprakash MR, Singhi S, et al. Recent experience with fungaemia: change in species distribution and azole resistance. *Scand J Infect Dis* 2009; 41:275-84.
- 12 Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Akdagli S, Bille J, Donnelly JP, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: diagnostic procedures. *Clin Microbiol Infect.* 2012; 18 Suppl 7:9-18
- 13 Leaw SN, Chang HC, Barton R, Bouchara JP, Chang TC. Identification of medically important *Candida* and non-*Candida* yeast species by an oligonucleotide array. *J Clin Microbiol* 2007; 45:2220-9.
- 14 Martínez-Jiménez MC, Muñoz P, Guinea J, Valerio M, Alonso R, Escribano P, et al. Potential role of *Candida albicans* germ tube antibody in the diagnosis of deep-seated candidemia. *Med Mycol* 2014; 52: 270-5.
- 15 Martínez-Jiménez MC, Muñoz P, Valerio M, Alonso R, Martos C, Guinea J, et al. *Candida* biomarkers in patients with candidaemia and bacteraemia. *J Antimicrob Chemother* 2015; 70: 2354-61.
- 16 Marchetti O, Lamothe F, Mikulska M, Viscoli C, Verweij P, Bretagne S, et al. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. *Bone Marrow Transplant* 2012; 47: 846-54.
- 17 Del Principe MI, Sarmati L, Cefalo M, Fontana C, De Santis G, Buccisano F, et al. A cluster of *Geotrichum clavatum* (*Saprochaete clavata*) infection in haematological patients: a first Italian report and review of literature. *Mycoses* 2016; 59 (9): 594-601.
- 18 Quiles-Melero I, García-Rodríguez J, Romero-Gómez MP, Gómez-Sánchez P, Mingorance J. Rapid identification of yeasts from positive blood culture bottles by pyrosequencing. *Eur J Clin Microbiol Infect Dis* 2011; 30: 21-4.
- 19 Hsiue HC, Huang YT, Kuo YL, Liao CH, Chang TC, Hsueh PR. Rapid identification of fungal pathogens in positive blood cultures using oligonucleotide array hybridization. *Clin Microbiol Infect* 2010;16(5): 493-500.
- 20 de Almeida JN Júnior, Sztajn bok J, da Silva AR Junior, Vieira VA, Galastri AL, Bissoli L, et al. Rapid identification of moulds and arthroconidial yeasts from positive blood cultures by MALDI-TOF mass spectrometry. *Med Mycol* 2016; 54: 885-9.
- 21 Patterson TF, Donnelly JP. New concepts in diagnostics for invasive mycoses: non-culture-based methodologies. *J Fungi (Basel)* 2019; 5: 9.
- 22 Ebricht JR, Fairfax MR, Vazquez JA. *Trichosporon asahii*, a non-*Candida* yeast that caused fatal septic shock in a patient without cancer or neutropenia. *Clin Infect Dis* 2001; 33: E28-30.
- 23 Camus V, Thibault ML, David M, Gargala G, Compagnon P, Lamoureaux F, et al. Invasive *Geotrichum clavatum* fungal infection in an acute myeloid leukaemia patient: a case report and review. *Mycopathologia* 2014; 177(5-6): 319-24.
- 24 Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA, Lortholary O; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. *Clin Microbiol Infect* 2014; 20 Suppl 3:76-98.
- 25 Desnos-Ollivier M, Blanc C, Garcia-Hermoso D, Hoinard D, Alanio A, Dromer F. Misidentification of *Saprochaete clavata* as *Magnusiomyces capitatus* in clinical isolates: utility of internal transcribed spacer sequencing and matrix-assisted laser desorption ionization-time of flight mass spectrometry and importance of reliable databases. *J Clin Microbiol* 2014; 52(6):2196-8.
- 26 Martino R, Salavert M, Parody R, Tomás JF, de la Cámara R,

- Vázquez L, et al. *Blastoschizomyces capitatus* infection in patients with leukemia: report of 26 cases. *Clin Infect Dis* 2004; 38(3): 335-41.
- 27 Koç AN, Atalay MA, Timur D, Demir G, Kaynar L. Molecular epidemiology and antifungal susceptibility of *Saprochaete capitata* (*Blastoschizomyces capitatus*) isolates causing nosocomial infection in Kayseri/Turkey. *Infect Dis (Lond)* 2016; 48(8): 596-603.
- 28 Cavanna C, Lallitto F, Mangione F, Tamarozzi F, Marone P, Cerriana P. Fungemia due to *Saprochaete capitata* in a non-neutropenic patient hospitalized in an intensive care unit after cardiac surgery. *J Mycol Med* 2017; 27(2):281-284.
- 29 Celik AD, Ozaras R, Kantarcioglu S, Mert A, Tabak F, Ozturk R. Spondylodiscitis due to an emergent fungal pathogen: *Blastoschizomyces capitatus*, a case report and review of the literature. *Rheumatol Int* 2009; 29(10):1237-41.
- 30 Marie I, Ménard JF, Hachulla E, Chérin P, Benveniste O, Tiev K, et al. Infectious complications in polymyositis and dermatomyositis: a series of 279 patients. *Semin Arthritis Rheum* 2011; 41(1):48-60.
- 31 CNRMA 2018 activity report. <https://www.pasteur.fr/fr/sante-publique/CNR/les-cnr/mycoses-invasives-anti-fongiques/rapports-d-activite> (25/11/2019)
- 32 Vaux S, Criscuolo A, Desnos-Ollivier M, Diancourt L, Tarnaud C, Vandenbogaert M, et al. *Geotrichum* Investigation Group. Multicenter outbreak of infections by *Saprochaete clavata*, an unrecognized opportunistic fungal pathogen. *MBio* 2014; 5(6): pii: e02309-14.
- 33 Favre S, Rougeron A, Levoir L, Pérard B, Milpied N, Accoceberry I, et al. *Saprochaete clavata* invasive infection in a patient with severe aplastic anemia: Efficacy of voriconazole and liposomal amphotericin B with adjuvant granulocyte transfusions before neutrophil recovery following allogeneic bone marrow transplantation. *Med Mycol Case Rep* 2016;11:21-3.
- 34 Fernández-Ruiz M, Guinea J, Puig-Asensio M, Zaragoza Ó, Almirante B, Cuenca-Estrella M, et al. CANDIPOP Project; GEIH-GEMICOMED (SEIMC) and REIPI. Fungemia due to rare opportunistic yeasts: data from a population-based surveillance in Spain. *Med Mycol* 2017; 55(2):125-136.
- 35 Santino I, Bono S, Borruso L, Bove M, Cialdi E, Martinelli D, et al. *Kodamaea ohmeri* isolated from two immunocompromised patients: first report in Italy. *Mycoses* 2013; 56:179-81.
- 36 Alvarado Socarras J, Rojas Torres JP, Vargas Soler JA, Guerrero C. *Kodamaea ohmeri* infection in a newborn with a mediastinal mass. *Arch Argent Pediatr* 2016 Oct 1; 114(5):e319-22.
- 37 Tashiro A, Nei T, Sugimoto R, Watanabe A, Hagiwara J, Takiguchi T, et al. *Kodamaea ohmeri* fungemia in severe burn: Case study and literature review. *Med Mycol Case Rep* 2018; 22: 21-23.
- 38 Chakrabarti A, Rudramurthy SM, Kale P, Hariprasath P, Dhaliwal M, Singhi S. Epidemiological study of a large cluster of fungemia cases due to *Kodamaea ohmeri* in an Indian tertiary care centre. *Clin Microbiol Infect* 2014; 20(2):O83-9.
- 39 Lacroix C, Brethon B, Boissel N, Desnos M, Leblanc T, Raffoux E, et al. *Geotrichum clavatum* an emerging pathogen responsible for invasive infection in two neutropenic leukemia patients. abstract No: P180 Full conference title: 3rd Trends in Medical Mycology 2007, Italy, NULL Conference abstracts
- 40 Picard M, Cassaing S, Letocart P, Verdeil X, Protin C, Chauvin P, et al. Concomitant cases of disseminated *Geotrichum clavatum* infections in patients with acute myeloid leukemia. *Leuk Lymphoma* 2014; 55(5):1186-8.
- 41 Salguero Fernández I, Nájera Botello L, Orden Martínez B, Roustan Gullón G. Disseminated fungemia by *Saprochaete clavata*. *Enferm Infecc Microbiol Clin* 2018 13. pii: S0213-005X(18)30190-3.
- 42 Buchta V, Bolehovská R, Hovorková E, Cornely OA, Seidel D, Žák P *Saprochaete clavata* Invasive Infections - A New Threat to Hematological-Oncological Patients. *Front Microbiol* 2019; 10:2196.
- 43 Liu X, Zhou W, Jiang Y, Kuang L. Invasive Fungal Infection Caused by *Geotrichum clavatum* in a Child with Acute Leukemia: First Documented Case from Mainland China. *Jpn J Infect Dis* 2019; 72(2):130-132.
- 44 Leoni M, Riccardi N, Rotulo GA, Godano E, Faraci M, Bandettini R, et al. *Magnusiomyces clavatus* infection in a child after allogeneic hematopoietic stem cell transplantation: Diagnostic and therapeutic implications. *Med Mycol Case Rep* 2018; 23:65-67.
- 45 Stanzani M, Cricca M, Sassi C, Sutto E, De Cicco G, Bonifazi F, et al. *Saprochaete clavata* infections in patients undergoing treatment for haematological malignancies: A report of a monocentric outbreak and review of the literature. *Mycoses* 2019; 62(12):1100-1107.
- 46 Wee LWY, Ling HY, Chong CY, Soe MN, Koh MJA. A rare case of purpuric rash caused by *Saprochaete clavata* in a pediatric patient with acute leukemia. *Pediatr Dermatol* 2019; 36(6):990-991.
- 47 P. Pavone, A. Oliva, G. Raponi, F. Pugliese, S. Martelli, P. Celli, et al. Disseminated fungal infection due to *Saprochaete clavata* in a kidney transplant recipient. *Journal de Mycologie Médicale* 2019; 29, 278-82.