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Review

Spectrum and management of rare *Candida*/yeast infections in Kuwait in the Middle East

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Suhail Ahmad, Mohammad Asadzadeh, Noura Al-Sweih and Ziauddin Khan

***Abstract*:** Invasive fungal infections (IFIs) are associated with high mortality rates and mostly affect patients with compromised immunity. The incidence of IFIs is increasing worldwide with the expanding population of susceptible patients. *Candida* and other yeast infections represent a major component of IFIs. Rare *Candida*/yeast infections have also increased in recent years and pose considerable diagnostic and management challenges as they are not easily recognized by routine phenotypic characteristic-based diagnostic methods and/or by the automated yeast identification systems. Rare *Candida*/yeasts also exhibit reduced susceptibility to antifungal drugs making proper management of invasive infections challenging. Here, we review the diagnosis and management of 60 cases of rare *Candida*/yeast IFIs described so far in Kuwait, an Arabian Gulf country in the Middle East. Interestingly, majority (34 of 60, 56.7%) of these rare *Candida*/yeast invasive infections occurred among neonates or premature, very-low-birth-weight neonates, usually following prior bacteremia episodes. The clinical details, treatment given, and outcome were available for 28 of 34 neonates. The crude mortality rate among these neonates was 32.2% as 19 of 28 (67.8%) survived the infection and were discharged in healthy condition, likely due to accurate diagnosis and frequent use of combination therapy. Physicians treating patients with extended stay under intensive care, on mechanical ventilation, receiving broad spectrum antibiotics and with gastrointestinal surgery/complications should proactively investigate IFIs. Timely diagnosis and early antifungal treatment are essential to decrease mortality. Understanding the epidemiology and spectrum of rare *Candida*/yeast invasive infections in different geographical regions, their susceptibility profiles and management will help to devise novel diagnostic and treatment approaches and formulate guidelines for improved patient outcome.

Keywords: invasive infections, Kuwait, Middle East, rare *Candida*/yeast, treatment and outcome

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Introduction

Invasive fungal infections (IFIs) mostly affect individuals with compromised immunity such as patients living with human immunodeficiency virus (HIV), patients with cancer receiving chemotherapy, and organ transplant recipients in tertiary care settings and are associated with considerable morbidity and high mortality rates.[1–3] The progress in medical and surgical procedures during the last three decades and increasing use of antifungal prophylaxis have managed to prolong the survival of critically ill patients at the extremes of age (neonates and >65-year-old subjects) in intensive care unit (ICU) settings but have also resulted in expanding the number of patients susceptible to IFIs.[4–7] *Candida* and other yeasts are a significant cause of IFIs worldwide.[8–13] Epidemiological studies carried out in many countries including Kuwait have shown that nearly 92% of all *Candida*/yeast invasive

Correspondence to:
Suhail Ahmad
Department of Microbiology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait
suhail.ahmad@ku.edu.kw

Mohammad Asadzadeh
Noura Al-Sweih
Ziauddin Khan
Department of Microbiology, Faculty of Medicine, Kuwait University, Jabriya, Kuwait

infections are caused by only five species comprising *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Nakaseomyces glabratus* (also known as, aka, *Candida glabrata*), and *Pichia kudriavzevii* (aka *Candida krusei*), while rare *Candida*/yeast species usually cause <1% of all invasive yeast infections.[14–17] Although *C. albicans* is the most common causative agent of invasive candidiasis in susceptible patients, majority of *Candida* infections are now caused by non-*albicans Candida* or other yeast species in many geographical settings.[11,14–18] Recent years have also witnessed the emergence of many rare *Candida*/yeasts as human pathogens.[11,19–22] Severely ill patients with prior immunosuppression, mechanical ventilation, total parenteral nutrition, hematological malignancies, and chronic lung disease have been shown to be more prone to develop fungemia due to rare yeasts.[20–26]

Recent emergence of *Candida auris*, a growing health threat, has been phenomenal and is attributed to its environmental adaptation to increasing temperatures as a result of the global warming, which have allowed it to tolerate mammalian thermal barrier.[27–31] Although initially identified only in 2009,[32] *C. auris* has spread rapidly across various countries on all inhabited continents and has also caused major outbreaks in health care facilities that have been very difficult to control and manage clinically, chiefly due to its often multidrug-resistant nature.[33–36] Other multidrug-resistant yeasts have also emerged in recent years and include *N. glabratus*, *P. kudriavzevii*, *Meyerozyma guilliermondii* (aka *Candida guilliermondii*), *Candida haemulonii* species complex, *Clavispora lusitaniae* (aka *Candida lusitaniae*) and *Kluyveromyces marxianus* (aka *Candida kefyr*).[37–42]

Rare *Candida*/yeast infections pose considerable diagnostic and management challenges as they are not easily recognized by routine diagnostic laboratory procedures based on phenotypic characteristics including growth on chromogenic media.[20–22,43–47] Automated systems such as Vitek 2 yeast identification system (Vitek 2) or matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF MS) tests such as Vitek MS also occasionally fail to identify rare yeast species accurately due to lack of reference data warranting identification by molecular methods.[21,47–50] Rare *Candida*/yeast species also exhibit reduced susceptibility to one or more antifungal drugs.[20–22,50] Furthermore, pediatric patients and neonates compared to adults are distinct in terms of predisposing factors, disease presentation and epidemiology of *Candida*/yeast invasive diseases, and in their response to antifungal drugs.[14,15,18] Thus, proper treatment of rare yeast invasive infections is extremely challenging and so these infections are usually associated with higher mortality rates compared to infections by other more common *Candida*/yeast species.[20–22,47]

Kuwait is an Arabian Gulf country in the Middle East. Kuwaiti nationals comprise only about one-third of the total population of nearly 4 million individuals. The remaining subjects are expatriate residents originating from >50 countries. The vast majority of the expatriates originate from developing countries of South Asia (mainly India, Bangladesh, Pakistan, Nepal, and Sri Lanka), Southeast Asia (mainly the Philippines) and Africa (mainly Egypt, Sudan, and Ethiopia).[51,52] The laboratory capacity building during the beginning of the new millennium and the establishment of a dedicated mycology laboratory within the Department of Microbiology, Faculty of Medicine, Kuwait University employing state-of-the-art molecular diagnostic procedures enabled us to accurately identify rare *Candida*/yeast pathogens isolated from various clinical specimens of patients hospitalized in different government hospitals in Kuwait. In this article, we present an overview of the diagnosis and management of invasive *Candida*/yeast infections described so far in Kuwait. In order to keep pace with recent developments,[42] we have first described the infections caused by rare *Candida* species followed by infections by yeast species previously included among *Candida* genus and concluded the write-up by including infections by other rare yeast species. The cumulative clinical details, diagnostic methods needed for identification, antifungal treatment duration, and outcome for patients with rare *Candida*/yeast infections are presented in Table 1. Patient-specific details are provided in Supplemental Table S1. The antifungal susceptibility testing (AST) data for rare *Candida*/yeast isolates described here are shown in Table 2. We also briefly discuss the new antifungal drug pipeline that may help in reducing the mortality from rare *Candida* /yeast infections in the future.

Invasive infections caused by rare *Candida* species

C. dubliniensis *candidemia*

C. dubliniensis, a pathogenic yeast species closely related to *C. albicans* was identified as a distinct species in 1995.[74] Although *C. dubliniensis* is prevalent throughout the world, it is usually found as oral carriage or causes oropharyngeal infection in people living with HIV but rarely occurs in the oral microflora of normal healthy subjects.[75] While *C. albicans* is usually the dominant cause of candidemia, *C. dubliniensis* causes <1% of candidemia cases.[14,16,76] Since *C. albicans* and *C. dubliniensis* share many phenotypic characteristics including germ-tube formation, differential media such as sunflower seed agar and tobacco agar have been developed for their rapid differentiation in routine diagnostic laboratories.[77,78] The clinical details, antifungal treatment given and outcome were described for 11 of 14 candidemia patients diagnosed during 2002–2010 in an earlier study[53] and an additional case was described more recently.[19] All (including six elderly and three pediatric) patients were immunocompromised subjects with one to several risk factors for IFIs (Table 1 and Supplemental Table S1). All isolates were uniformly susceptible to all antifungal agents tested except one isolate that was resistant to 5-flucytosine (Table 2).

Although all bloodstream isolates were correctly identified by phenotypic methods including germ-tube formation and colony characteristics on sunflower seed agar and the diagnosis was confirmed by Vitek 2 and molecular methods, 5 of 12 patients expired including 4 with central venous catheter (Table 1). The high mortality was likely due to multiple comorbidities and other risk factors, prior episodes of bacteremia and delays in specific diagnosis as two patients died before culture results became available and another two died soon after the commencement of treatment (Supplemental Table S1).[19,53] Treating physicians should consider *C. dubliniensis* as one of the possible pathogens causing catheter-related infections for rapid diagnosis and improved outcome. Late complications and fatal outcome have also been reported in patients whose blood cultures had become negative for *C. dubliniensis* after antifungal therapy.[79,80]

Mini outbreak of candidemia due to C. haemulonii

C. haemulonii species complex comprises several rare and recently described species such as *C. haemulonii*, *C. duobushaemulonii*, *C. pseudohaemulonii*, and *C. vulturna* and the notorious multidrug-resistant pathogen, *C. auris*.[35,41,81] These organisms colonize humans in the community and hospital settings and many clinical isolates show reduced susceptibility to one or more antifungal drugs.[41,81] *Candida khanbhai*, another novel species closely related to *C. haemulonii* complex, isolated from the nasal swab sample in Kuwait and bloodstream of a candidemia patient in Malaysia, has also been described recently.[82] Interestingly, colonies of *C. khanbhai* on CHROMagar Candida Plus medium are indistinguishable from *C. auris*.[82]

The first documented candidemia case by *C. haemulonii* occurred in a nearly full-term, neonate who had been in the neonatal ICU (NICU) for 42 days, had received broad-spectrum antibiotics for multiple episodes of bacteremia and was on mechanical ventilator and total parenteral nutrition through central lines (Table 1 and Supplemental Table S1). While this patient was in the NICU, three other premature, very-low-birth-weight (VLBW) neonates who were in the same NICU for 30 to 76 days with multiple episodes of bacteremia also developed *C. haemulonii* fungemia resulting in a mini outbreak (Table 1). Repeat isolates were obtained from cases 3 and 4. The isolates were identified as *Rhodotorula glutinis* by the Vitek 2 and as *C. haemulonii* by PCR-sequencing of the internal transcribed spacer (ITS) region and D1/D2 domains of rDNA.[54] CHROMagar Candida™ supplemented with Pal's medium is now available for phenotypic identification of *C. haemulonii*.[83] All isolates showed reduced *in vitro* susceptibility to amphotericin B, fluconazole, and itraconazole (Table 2).[54] Two of four neonates survived the infection including one case treated with fluconazole alone even though the isolate showed *in vitro* resistance to this drug (Table 1 and Supplemental Table S1).[54] This is consistent with other reports showing successful treatment of fungemia cases caused by both, *in vitro* fluconazole-susceptible and -resistant strains by fluconazole therapy.[84,85] Treatment with amphotericin B is not very effective against *C. haemulonii*[84] as is also evident by fatal outcome of the neonate in Case 3 (Supplemental Table S1).

Table 1. Brief summary of clinical details, treatment duration and outcome for patients with rare *Candida*/yeast invasive infections.

Rare *Candida* or yeast species	Source of isolation	No. of patients affected	Sporadic cases or outbreak	Major underlying conditions	Other risk factors	Diagnostic methods needed for identification[b]				Antifungal treatment duration	Outcome or mortality rate	References
						Phenotypic	Vitek 2	Vitek MS	Molecular			
Candida species												
Candida dubliniensis	Blood	12	Sporadic	Cancer/leukemia, abdominal surgery	DM, CVC, BSA, TPN, MV	Adequate	Adequate	Confirmatory	Confirmatory	3–64 days	5 of 12 expired	19, 53
Candida haemulonii	Blood	4	Outbreak	PM, VLBW	Extended stay in NICU, BSA, TPN, MV	Adequate	Adequate	Confirmatory	Confirmatory	14–80 days	2 of 4 expired	54
Candida auris	Blood, urine, TS	2	Sporadic	Respiratory or renal failure	DM, BSA, antifungal prophylaxis	Adequate	Adequate	Confirmatory	Confirmatory	1–24 days	2 of 2 expired	55 and 56
Candida metapsilosis	Blood	1	Sporadic	Encephalopathy, bronchopneumonia	CVC, Gastric tube feeding, MV	Inadequate	Inadequate	Adequate	Confirmatory	0 days, catheter replaced	Survived	57
Candida blankii[a]	Blood	1	Sporadic	PM, VLBW	UVC, NEC, BSA, antifungal prophylaxis	Inadequate	Inadequate	Inadequate	Required	19 days	Expired	58
Candida conglobata[a]	Blood	1	Sporadic	PM, VLBW	HMD, UAC, UVC, MV, BSA, fluconazole prophylaxis	Inadequate	Inadequate	Inadequate	Required	60 days, catheter removal	Survived	59
Previously among *Candida* species												
Cyberlindnera fabianii[a]	Blood	14	Outbreak	PM, VLBW	ICU/NICU stay, UAC, UVC, MV, BSA	Inadequate	Suggestive	Adequate	Required	0–31 days	3 of 13 expired	19 and 60
Cl. lusitaniae	Blood, SF	12	Sporadic	PM, VLBW, IV drug use	Prior bacterial sepsis, BSA, CVC, UAC, UVC	Suggestive	Adequate	Confirmatory	Confirmatory	14–>29 days	3 of 12 expired	19, 61 and 62
K. marxianus[a]	Blood	1	Sporadic	Cardiac arrest, renal impairment	HTN, cholecyctectomy, CVC, BSA, MV	Inadequate	Adequate	Confirmatory	Confirmatory	11 days	Survived	63
Meyerozyma fermentati	Blood	1	Sporadic	PM, VLBW	HMD, UAC, UVC, PC, MV, BSA	Inadequate	Inadequate	Inadequate	Required	37 days	Survived	64

(Continued)

Table 1. (Continued)

Rare *Candida* or yeast species	Source of isolation	No. of patients affected	Sporadic cases or outbreak	Major underlying conditions	Other risk factors	Diagnostic methods needed for identification[b]				Antifungal treatment duration	Outcome or mortality rate	References
						Phenotypic	Vitek 2	Vitek MS	Molecular			
Non-*Candida* yeast species												
Lodderomyces elongisporus	Blood CVC tip	3	Sporadic	PM, VLBW, stroke, CVA, aspiration pneumonia	UAC, CVC, TPN, BSA, HTN, IHD, septic shock	Suggestive	Inadequate	Adequate	Confirmatory	1–10 days	2 of 3 expired	65–67
Magnusiomyces capitatus	Blood	3	Sporadic	Leukemia, respiratory failure, liver failure	DM, HTN, IHD, chemotherapy, MV, antifungal prophylaxis	Suggestive	Adequate	Confirmatory	Confirmatory	0–3 days	3 of 3 expired	68 and 69
Kodamaea ohmeri	Blood	2	Sporadic	PM, VLBW, old age	Prior bacterial sepsis, BSA, respiratory distress	Inadequate	Adequate	Confirmatory	Confirmatory	0–28 days	1 of 2 expired	19 and 70
Rhodotorula mucilaginosa	Blood	1	Sporadic	Acute lymphocytic leukemia	Blood/platelet transfusions, chemotherapy, CVC	Inadequate	Suggestive	Adequate	Confirmatory	21 days	Survived	71
Malassezia pachydermatis	Blood	1	Sporadic	PM, VLBW	UVC, TPN, BSA, MV	Inadequate	Suggestive	Adequate	Confirmatory	7 days	Survived	72
Papiliotrema laurentii[a]	Blood	1	Sporadic	PM, VLBW	UVC, NEC, TPN, BSA	Inadequate	Adequate	Confirmatory	Confirmatory	14 days	Survived	73

[a]Multiple isolates were recovered from some patients with persistent fungemia.
[b]Phenotypic methods usually identify yeast species based on colony characteristics on differential growth media such as sunflower seed agar, tobacco agar, CHROMagar Candida, and CHROMagar Candida plus. Vitek 2 (and others such as ID32C and API 20C AUX) yeast identification system and Vitek MS based on protein profiles identify yeasts based on their reference databases that are being constantly updated. Molecular methods may include PCR, multiplex PCR, real-time PCR-based assays and PCR-sequencing of rDNA.
ABMT, allogeneic bone-marrow transplantation; BSA, broad-spectrum antibiotics; CVC, central venous catheter; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; IHD, ischemic heart disease; IV, intravenous; MPS, mucopolysaccharidosis; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; CVA, cardiovascular attack; PM, premature; SF, synovial fluid; TPN, total parenteral nutrition; TS, tracheal secretions; UAC/UVC, umbilical arterial/venous catheter; VLBW, very-low-birth-weight.

Table 2. Antifungal susceptibility testing data for rare *Candida*/yeast isolates.

Rare *Candida*/ yeast species	Source of isolation	No. of isolates	AST method	Minimum inhibitory concentration (MIC) value or MIC range (μg/mL) for									Reference
				AMB	FLU	VOR	ITR	POS	CFG	AFG	MFG	5-FC	
C. dubliniensis	Blood	12	Etest	0.002–0.125	0.125–0.5	0.004–0.19	N.D.	0.008–0.016	0.003–0.064	N.D.	N.D.	0.004-**⩾32**	19, 53
C. haemulonii	Blood	4	Etest	**4.0–6.0**	**96–⩾256**	0.047–0.38	**2.0–3.0**	N.D.	0.125–0.5	N.D.	N.D.	0.032–0.064	54
C. auris	Blood	1	Etest	0.064	**>256**	0.38	N.D.	N.D.	0.064	N.D.	N.D.	N.D.	55
C. auris	Blood, urine, TS	7*	MCN-AM	1	**>128**	0.25–5	0.5–1.0	0.031–0.063	N.D.	0.016–1.0	0.016–1.0	N.D.	56
C. metapsilosis	Blood	1	Etest	0.094	0.75	0.023	N.D.	N.D.	0.125	N.D.	N.D.	0.023	57
C. blankii	Blood	4*	Etest	0.125	12.0–16.0	0.19–0.38	0.75	0.5–0.75	0.25–0.5	0.19	0.125	N.D.	58
C. conglobata	Blood	6*	Etest	0.002–0.064	0.38–1.0	0.002–0.047	N.D.	N.D.	0.023–0.19	0.008–0.012	0.064–0.125	0.002	59
Cy. fabianii	Blood	10	Etest	0.016–0.75	1.0–**4.0**	0.047–0.094	1.5–**24.0**	0.125–**4.0**	0.008–0.125	0.004–0.047	0.047–0.094	0.016–0.094	60
Cy. fabianii	Blood	4	Etest	0.064–0.5	1.5–**6.0**	0.064–0.19	N.D.	N.D.	0.047–0.38	N.D.	N.D.	N.D.	19
Cl. lusitaniae	Blood, SF	12	Etest	0.002–0.096	0.19–1.5	0.003–0.023	N.D.	N.D.	0.012–0.25	N.D.	0.032–0.125	N.D.	19, 61 and 62
K. marxianus	Blood	2*	Etest	0.094–0.125	0.094	0.004–0.008	0.023	0.002–0.012	0.094	0.002–0.016	0.064–0.094	0.047–0.094	63
M. fermentati	Blood	6*	Etest	0.002–0.125	3.0–4.0	0.125–0.38	3.0–4.0	0.19–0.25	0.125–0.75	N.D.	0.25–0.75	0.003–0.016	64
L. elongisporus	Catheter tip	1	Etest	N.D.	0.32	0.002	N.D.	0.023	0.094	N.D.	N.D.	0.094	65
			MCN-AM	0.13	0.25	⩽0.008	⩽0.03	⩽0.008	0.03	0.02	0.02	⩽0.006	
L. elongisporus	Blood	1	Etest	0.012	0.125	0.004	0.008	0.003	0.064	N.D.	0.003	0.064	66
			MCN-AM	0.06	⩽0.002	⩽0.008	⩽0.03	⩽0.008	0.03	0.02	0.02	⩽0.006	
L. elongisporus	Blood	1	MCN-AM	0.5	0.25	⩽0.008	⩽0.03	⩽0.008	0.03	0.02	0.02	⩽0.006	67
M. capitatus	Blood, urine, TS	3*	Etest	0.094–0.19	0.75–1.0	0.094–0.25	N.D.	N.D.	**>32**	N.D.	N.D.	N.D.	68
M. capitatus	Blood	2	Etest	0.5	**3–16**	0.19	N.D.	N.D.	**>32**	N.D.	**>32**	N.D.	69
K. ohmeri	Blood	1	Etest	0.023	**4**	0.047	0.125	0.012	0.25	0.064	0.125	0.032	70
K. ohmeri	Blood	1	Etest	0.008	**256**	0.19	N.D.	N.D.	0.19	N.D.	N.D.	N.D.	19
R. mucilaginosa	Blood	3*	Etest	0.023	**>256**	**2**	N.D.	**>32**	**>32**	N.D.	N.D.	0.016	71
M. pachydermatis	Blood	1	Etest	0.19	**>256**	0.012	N.D.	0.016	**>32**	N.D.	N.D.	**>32**	72
P. laurentii	Blood	2*	Etest	0.047	2.0–8.0	0.047–0.094	N.D.	N.D.	32	N.D.	N.D.	N.D.	73

Values indicative of reduced susceptibility/resistance are shown in bold.
*Multiple isolates from the same patient from the same or different sites.
AFG, andulafungin; AMB, amphotericin B; AST, antifungal susceptibility testing; CFG, caspofungin; 5-FC, 5-flucytosine; FLU, fluconazole; ITR, itraconazole; MCN-AM, MICRONAUT-AM EUCAST broth microdilution-based method; MFG, micafungin; N.D., not done; POS, Posaconazole; SF, synovial fluid; TS, tracheal secretion; VOR, voriconazole.

Other *C. haemulonii* complex members (e.g. *C. duobushaemulonii*) have also been isolated from blood samples of hospitalized patients in Kuwait but the clinical details and treatment given were not available.[86]

C. haemulonii invasive infections are more common in developing countries in tropical regions. This yeast colonizes the skin, predominantly in women, and catheters provide the main portal of entry for fungemia.[81] Physicians treating neonates in tropical areas should consider the diagnosis of *C. haemulonii* fungemia and treatment should include, if echinocandins are not available, fluconazole or other azoles, even if the isolate exhibits reduced *in vitro* susceptibility.[84,85]

Emergence, spread and outbreak of C. auris *infections in Kuwait*

C. auris is a recently recognized yeast that was first isolated from the ear canal of a female patient in Japan in 2009 but soon spread to many other countries.[32,87] This novel yeast has attracted worldwide attention as many isolates exhibit reduced susceptibility to azoles and/or amphotericin B resulting in multidrug-resistant status of many strains and has been recognized as an urgent threat to public health by the Centers for Disease Control and Prevention (CDC) of USA.[30] This notorious organism has been isolated from >50 countries worldwide and has also caused outbreaks in healthcare facilities with devastating results and significant infection control challenges.[35,88] Two *C. auris* fungemia cases are noteworthy and their details together with other important development are briefly included in this review. The first case of *C. auris* fungemia in Kuwait was diagnosed in May, 2014 in a 27-year-old female (Table 1 and Supplemental Table S1). She was being treated with broad-spectrum antibiotics for septic shock when she developed fungemia.[55] The blood culture yeast isolate was initially identified as *C. haemulonii*, reflecting the inability of Vitek 2 in 2014 to correctly identify it or other rare/emerging yeast pathogens. Species-specific identification was achieved by PCR-sequencing of the ITS region of rDNA. *In vitro* AST data showed that the isolate was resistant to fluconazole but was susceptible to voriconazole, caspofungin, and amphotericin B (Table 2). Although the treatment was started with liposomal amphotericin B (150 mg/day), the patient died soon afterward from multiorgan failure.[55]

The initial isolation in 2014 was followed by identification of other *C. auris* isolates. A retrospective study identified 158 of 166 isolates, forming pink-colored colonies on CHROMagar Candida and identified as *C. haemulonii* by Vitek 2, as *C. auris*.[86] *C. auris* spread rapidly thereafter and was isolated from all major government hospitals except Maternity Hospital within 4 years of its first isolation in Kuwait.[89] The *C. auris* outbreak, which started in a major secondary care hospital, could only be contained but not eradicated despite intensive infection control measures.[33] By 2018, it had emerged as a major bloodstream yeast pathogen, surpassing the fourth ranked *N. glabratus*.[19] Patients with *C. auris* candidemia had multiple comorbidities, the duration of hospital stay before onset of fungemia varied from 5 to 93 days and the mortality was >50%, which is consistent with the data reported from other countries.[30,33,90] All *C. auris* isolates in Kuwait were resistant to fluconazole and bloodstream isolates were generally susceptible to amphotericin B and echinocandins.[33,89] However, some urine and respiratory isolates exhibited reduced susceptibility to echinocandins and amphotericin B and high-level amphotericin B resistance was shown to involve *ERG6* gene alterations and concomitant changes in total cell sterol profiles.[3,33,89,91] A whole genome sequence-based recent study also showed that resistance to echinocandins due to *FKS* mutations developed in patients during treatment.[92] The second important *C. auris* fungemia case in Kuwait involved multiple isolates from an immunocompromised patient with chronic lung transplant rejection (Table 1 and Supplemental Table S1).[56] This study showed that echinocandin resistance due to multiple genotypes may emerge in the same patient during treatment that is consistent with recent recommendations of multiple colony AST for proper management of invasive *Candida* infections.[56,93]

Some recent findings regarding *C. auris* invasive infections are noteworthy and treating physicians and microbiologists should be aware of these developments. Timely diagnosis and accurate AST of *C. auris* is crucial for effective management of invasive infections. Accurate diagnosis even in resource-limited settings is now greatly facilitated by the development of phenotypic methods such as CHROMagar Candida Plus, expanded databases of Vitek 2 and Vitek MS, and a variety of molecular

methods.[30,46,83] The *in vitro* AST data should be interpreted with caution as several, particularly commercial, methods either overestimate or underestimate resistance of *C. auris* to fluconazole and amphotericin B.[94,95]

C metapsilosis *fungemia*

C. metapsilosis and *C. orthopsilosis* together with *C. parapsilosis* form the *C. parapsilosis* complex. Simple species-specific PCR and/or multiplex PCR assays were developed in Kuwait to identify the two cryptic species in *C. parapsilosis* sensu lato isolates.[96,97] These studies identified bloodstream infections by *C. orthopsilosis* but clinical details, treatment given and outcome were not reported.[96,97] Although initial studies did not detect invasive cases due to *C. metapsilosis*, one fungemia case in a 10-year-old female was subsequently detected.[57] She had progressive encephalopathy, epilepsy, and developed bronchopneumonia in the pediatric ICU (PICU). Other risk factors included CVC, mechanical ventilation, endotracheal tube placement, and gastric feeding (Table 1). The blood culture isolate was initially identified as *C. parapsilosis* by colony characteristics on CHROMagar Candida and Vitek 2 but was later confirmed as *C. metapsilosis* by PCR-sequencing of the ITS region of rDNA (Supplemental Table S1).[57] The isolate was susceptible to the antifungal drugs tested (Table 2). The catheter was removed but she did not receive any specific antifungal treatment and survived the infection. However, she subsequently had episodes of bronchopneumonia and candidemia due to *C. albicans* and eventually expired.

C. metapsilosis colonizes the skin and oral cavity that may provide the source of infection in individuals with catheters and/or mechanical ventilation. Specific identification is achieved by Vitek MS or molecular methods and catheter removal may suffice in most cases, as was noted in this case, since this is the least virulent member of the *C. parapsilosis* complex.[98]

C. blankii *fungemia*

C. blankii, a non-fermenting yeast mostly used in biotechnological research, is an emerging, often fatal, opportunistic pathogen that recently caused an outbreak among low/VLBW neonates in India.[99,100] *C. blankii* usually has lower susceptibility to azoles and may also exhibit reduced susceptibility to echinocandins or amphotericin B.[99–101] A case of persistent fungemia due to *C. blankii* has also been described from Kuwait in a preterm, VLBW neonate receiving antifungal prophylaxis during multiple episodes of bacteremia (Table 1).[58] He was also empirically treated twice with liposomal amphotericin B (AmBisome) (Supplemental Table S1). He later developed persistent septicemia due to a bacterial and a yeast pathogen, the latter initially forming pink and subsequently dark metallic blue colonies (similar to *C. tropicalis*) on CHROMagar Candida. It was identified as *Stephanoascus ciferii* by Vitek 2 and as *C. blankii* by PCR-sequencing of rDNA.[58] Despite treatment with AmBisome for 16 days and then with AmBisome plus caspofungin for 5 days in addition to broad-spectrum antibiotics, the neonate expired due to polymicrobial septicemia (Table 1). The AST data showed that the isolates exhibited reduced susceptibility to fluconazole (minimum inhibitory concentration, MIC 12–16 μg/mL) but appeared susceptible to other antifungal drugs by Etest (Table 2).[58]

Isolation of yeast during breakthrough infection from VLBW neonates with the yeast initially forming pink and subsequently dark metallic blue colonies on CHROMagar Candida and showing clusters of budding yeast with pseudohyphae during slide culture on cornmeal agar should alert microbiologists to use molecular methods to confirm its identification.

C. conglobata *fungemia*

The first case of persistent *C. conglobata* bloodstream infection occurred in a preterm, VLBW (930 g) male neonate in Kuwait and the etiologic role of *C. conglobata* in bloodstream infection was proven unequivocally for the first time (Table 1 and Supplemental Table S1).[59] He had two episodes of bacteremia requiring treatment with broad-spectrum antibiotics and was given fluconazole empirically before blood culture from peripheral vein yielded a yeast that was identified as *M. farinosa* by Vitek 2 and as *C. conglobata* by PCR-sequencing of the ITS region and D1/D2 domains of rDNA.[59] The diagnosis was further confirmed by detection of *C. conglobata* DNA in serum samples. Despite treatment with AmBisome for 7 days, blood culture was still positive and so caspofungin was added to the treatment regimen (Supplemental Table S1). Although the blood sample collected on Day-6 post combination

therapy was positive for *C. conglobata* DNA by PCR and blood cultures were also positive for *C. conglobata* after 7-days and 17-days post combination therapy, the overall condition of the baby improved. The AST data showed that *C. conglobata* isolates appeared susceptible to amphotericin B, azoles, echinocandins, and 5-flucytosine (Table 2). The catheters were removed on Day-18 post combination therapy. The blood cultures eventually became negative after continued treatment with AmBisome and caspofungin for 25 days, and the baby was discharged with a weight of 2690 g in a healthy condition (Table 1).[59]

Isolation of yeast during breakthrough infection from VLBW neonates with the yeast forming pink colonies on CHROMagar Candida[86] and showing well-branched pseudohyphae with budding yeast during culture on cornmeal agar[59] should prompt microbiologists to use molecular methods to confirm its identification for appropriate treatment.

Invasive infections caused by yeasts recently removed from the genus *Candida*

C. fabianii *fungemia cases in Kuwait*

Cyberlindnera fabianii (aka *Candida fabianii*) is an environmental ascomycetous yeast that is found in soil and is used in wastewater treatment and fermentation of alcoholic beverages. *Cy. fabianii* colonizes the skin and vagina and is an opportunistic pathogen capable of causing bloodstream infections in patients with severe immunosuppression, major surgery, and treatment with broad-spectrum antibiotics.[23,102–104] Neonates with low birth weight appear to be particularly susceptible to developing invasive infections.[105–108] *Cy. fabianii* is an emerging yeast pathogen in the Middle East, forms antifungal drug-resistant biofilms and acquires resistance to fluconazole and other drugs rapidly, which allow this yeast to breakthrough antifungal prophylaxis and empiric treatment.[102,104,107–110]

Cy. fabianii has caused several invasive infections, mostly among neonates including a fungemia outbreak among premature, VLBW neonates in the Maternity Hospital in Kuwait.[19,60] The clinical details were available for 14 cases and outcome for 13 cases including all 10 neonates of the outbreak in 2014 (Table 1 and Supplemental Table S1). All neonates involved in the outbreak were on mechanical ventilation in the NICU, had umbilical catheters in place, and were receiving broad-spectrum antibiotics for suspected or confirmed bacteremia when the blood cultures yielded yeast, which was identified as *C. utilis* by Vitek 2 and as *Cy. fabianii* by Vitek MS and by PCR-sequencing of the ITS region and D1/D2 domains of rDNA (Table 1). All isolates appeared susceptible to amphotericin B, voriconazole, caspofungin, anidulafungin, and micafungin but showed reduced susceptibility to fluconazole, itraconazole, and posaconazole (Table 2).[60] Fungemia persisted in 6 of 10 neonates as multiple blood culture isolates were recovered, the central venous catheter tips from five neonates also yielded *Cy. fabianii* and blood samples from three neonates were also positive for *Cy. fabianii* DNA by PCR (Supplemental Table S1).[60] One neonate expired before blood cultures became positive while nine neonates received treatment with amphotericin B alone ($n=4$) or combination therapy ($n=5$) and eight of nine neonates survived the infection (Supplemental Table S1). Genotypic relatedness among outbreak isolates was indicated based on data obtained by microsatellite-based and minisatellite-based primers[111] and DNA sequence comparisons of the non-transcribed spacer (NTS-1) between 28S rRNA and 5S rRNA genes.[60]

Surveillance cultures from the NICU staff and environment were negative. Although the source of infection was not detected, the outbreak subsided with rigorous hand washing practice and strict compliance with standard infection control measures.[60] However, sporadic cases continued to occur and four other fungemia cases were described subsequently in ICU patients including three patients (a neonate, an infant, and a child) from Maternity Hospital in 2018 (Supplemental Table S1).[19] The isolates showed reduced susceptibility to fluconazole but appeared susceptible to voriconazole, caspofungin, and amphotericin B (Table 2). One patient expired before blood culture results became available, while two neonates treated with amphotericin B alone or combination therapy survived the infection. The outcome was not known for another neonate treated with amphotericin B alone (Supplemental Table S1).[19]

Phenotypic methods and Vitek 2 are inadequate for specific identification. *Cy. fabianii* appeared as ovoid to elongated cells, singly or in pairs, formed white to pink colored colonies on CHROMagar Candida and slide culture on cornmeal agar

showed budding yeast cells with pseudohyphae. Rapid identification by Vitek MS or by molecular methods and treatment with amphotericin B alone or in combination with other drugs may help in reducing mortality from invasive *Cy. fabianii* infections.[19,104,60]

Invasive Cl. lusitaniae *infections*

Clavispora lusitaniae (aka *Candida lusitaniae*) is an emerging opportunistic yeast pathogen that usually affects immunocompromised/immunosuppressed individuals with comorbidities that include immature or compromised immune system, prolonged antibiotic therapy and underlying malignancies, chemotherapy, or bone marrow transplants.[112] *Cl. lusitaniae* causes nearly 19% of fungemia cases in cancer patients. Although it has lower pathogenic potential and the mortality rate of invasive *Cl. lusitaniae* infections is usually <5%, some isolates exhibit resistance to amphotericin B.[112] However, none of 28 invasive isolates in Kuwait came from cancer patients and all isolates appeared susceptible to amphotericin B.[61,62]

The first documented case of invasive *Cl. lusitaniae* infection in Kuwait was described in a 29-year-old intravenous drug user and the isolate from synovial fluid was identified as *Cl. lusitaniae* by Vitek 2.[61] Presence of *Cl. lusitaniae* DNA and high levels of (1–3)-β-D-glucan in synovial fluid supported the diagnosis. Initial treatment with amphotericin B (0.7 mg/kg) including three intra-articular injections was not very effective. Complete cure was achieved by removal of the inflamed tissue by synovectomy and therapy with fluconazole (Supplemental Table S1).[61]

In a retrospective study of 990 available bloodstream isolates, 25 (2.5%) were identified as *Cl. lusitaniae* by Vitek 2, Vitek MS, and PCR amplification of rDNA.[62] Interestingly, 11 of 25 isolates were recovered from neonates with 9 isolates originating from a single hospital. The ITS region sequences of nine *Cl. lusitaniae* isolates showed six different haplotypes ruling out an outbreak by a dominant genotype.[62] The clinical details were available for eight of nine neonates. Additionally, 3 of 232 (1.3%) yeast fungemia cases due to *Cl. lusitaniae* were described 2018.[19] All *Cl. lusitaniae* isolates were susceptible to fluconazole, voriconazole, caspofungin, micafungin, and amphotericin B (Table 2). Treatment details and outcome were available for 11 neonates and 3 neonates including 2 twins expired giving an overall crude mortality rate of 27.3% (Supplemental Table S1).[62] All three neonates had one or more episodes of bacteremia and two neonates had bacterial septicemia prior to developing candidemia. *Cl. lusitaniae* has also been involved in bloodstream infections in neonates in Saudi Arabia, another Middle Eastern country in the Arabian Gulf region.[113] On the contrary, *Cl. lusitaniae* was not isolated from any of the 25 neonates, while eight cases of fungemia were detected among other pediatric patients in an international prospective study of invasive candidiasis.[114]

Phenotypic methods showing ovoid to subglobose budding yeast cells with abundant pseudohyphae and pink-colored colonies on CHROMagar Candida are suggestive, while Vitek 2 is adequate for specific identification of *Cl. lusitaniae*. All three neonates with unfavorable outcome received amphotericin B either alone or as primary therapy, while replacement of amphotericin B with fluconazole and/or caspofungin improved outcome.[62]

K. marxianus *fungemia*

Kluyveromyces marxianus (aka *Candida kefyr*), an ascomycetous yeast commonly found in kefir grains, plants, industrial sewage, and fermented dairy products, is an emerging pathogen in immunocompromised patients particularly those with oncohematological diseases.[21,42] Consumption of poorly refrigerated dairy products with overgrowth of *K. marxianus* could be the source of infection and the invasion is usually through damaged mucosa of gastrointestinal tract (mucositis) in susceptible patients.[21,115] The first documented case of *K. marxianus* fungemia in Kuwait was described in a nonhematological 60-year-old patient with severe brainstem dysfunction. The blood culture isolate was correctly identified by Vitek 2 and the diagnosis was confirmed by detection of *K. marxianus* DNA by PCR and by elevated levels of 1,3-β-D-glucan and *Candida* mannan in serum samples (Table 1 and Supplemental Table S1).[63,116] The bloodstream isolates appeared susceptible to all antifungal drugs tested (Table 2). Treatment with fluconazole was preferred due to renal impairment. After 3 days of treatment, blood drawn through arterial catheter yielded *K. marxianus*, while blood drawn through peripheral vein was culture negative.

With continued treatment, the patient became afebrile and survived the infection.[63]

A retrospective study that mainly included immunocompromised/cancer patients from two tertiary care hospitals in Kuwait subsequently identified four other *K. marxianus* bloodstream isolates during 2011–2018.[117] Sketchy clinical details and outcome were available for two of four fungemia patients and both patients died during their hospitalization.[117] Interestingly, several urine and respiratory isolates exhibited reduced susceptibility to amphotericin B.[117] These isolates showed altered cell sterol contents due to mutations in *ERG2* or *ERG3* involved in ergosterol synthesis.[118] These studies established *ERG2* and *ERG3* as gene targets for amphotericin B resistance that has been occasionally reported among invasive *K. marxianus* isolates from immunocompromised patients including patients with hematological malignancies.[115,118]

Rapid diagnosis of *K. marxianus* fungemia is achieved by Vitek 2 and fluconazole/other azoles or echinocandins should be preferred over amphotericin B due to the possibility of reduced susceptibility to amphotericin B.[115,117]

M. fermentati *fungemia in a premature neonate*

Meyerozyma fermentati (aka *Candida fermentati*) closely related to *Meyerozyma guilliermondii* (aka *Candida guilliermondii*) and other yeast species such as *Wickerhamomyces anomalus* (aka *Candida pelliculosa*) previously included among the genus *Candida* have also been isolated from fungemia cases in Kuwait.[19,42,64] Members of *M. guilliermondii* complex usually show reduced susceptibility to fluconazole and echinocandins, invasive infections mostly occur in patients with malignancy, immunosuppressive therapy, and/or neutropenia and usually have a favorable outcome due to low virulence of these yeasts.[119,120] The first documented case of *M. fermentati* fungemia, identified as *Candida famata* by Vitek 2, occurred in a preterm, VLBW neonate (Table 1 and Supplemental Table S1).[64] PCR-sequencing of rDNA was required for correct identification. The culture from the long-line tip also yielded the same yeast.[64] The isolates were susceptible to amphotericin B, voriconazole, caspofungin, and micafungin but exhibited reduced susceptibility to fluconazole and itraconazole (Table 2). He was initially treated with amphotericin B but complete resolution of fungemia required extended duration of combination therapy with liposomal amphotericin B and caspofungin.[64] The clinical details, treatment given, and outcome were not available for the fungemia case due to *M. guilliermondii*.[19] The *W. anomalus* fungemia occurred in a 5-month-old infant, the isolate showed reduced susceptibility to fluconazole, and the patient was treated with liposomal amphotericin B for 14 days with favorable outcome.[19]

Although *Nakaseomyces glabratus* (aka *Candida glabrata*) is a major yeast pathogen in Kuwait[17] and increasing trends of reduced susceptibility to fluconazole, echinocandins, and amphotericin B have been reported,[121] invasive infections by other members of the complex, that is, *Nakaseomyces nivariensis* (aka *Candida nivariensis*) and *Nakaseomyces bracarensis* (aka *Candida bracarensis*) were not detected.[122] However, *N. nivariensis* was recently cultured from tracheal aspirate and was identified by molecular methods.[123]

Invasive infections caused by other rare yeast species

Invasive infections by other rare yeast species have also increased in recent years due to increasing number of seriously ill and immunocompromised patients and few of these rare yeasts are now regarded as emerging pathogens in some geographical locations including Kuwait.[26,124] A brief summary of the rare yeast invasive infections described so far in Kuwait are summarized below.

L. elongisporus *as an emerging bloodstream pathogen in Kuwait:*

L. elongisporus shares many phenotypic characteristics with *C. parapsilosis* complex members and so is often misidentified as *C. parapsilosis* by Vitek 2 or other yeast identification methods.[124] This yeast has been isolated from diverse sources such as citrus concentrate, soil, fermented food products, stored apples, pigeon excreta, marine fish, hospital environments, and human clinical samples including blood.[124,125] The first suspected case of fungemia in Kuwait occurred in 2008 (Table 1 and Supplemental Table S1).[65] The isolate cultured from the catheter tip was identified as *C. parapsilosis* by Vitek 2 and as *L. elongisporus* by PCR-sequencing of rDNA and was susceptible to antifungal drugs tested (Table 2). The patient

was successfully treated by removal of catheter and intravenous fluconazole (400 mg/day).[65] The inability to culture *L. elongisporus* from the blood samples was attributed to the transient nature of fungemia due to infrequent seeding from the catheter and the low culture positivity that is commonly seen even among patients with proven cases of invasive infections.[116] Unlike *C. parapsilosis* isolates, *L. elongisporus* forms turquoise blue colonies on CHROMagar Candida and long ellipsoidal shaped ascospores after 7–10 days of incubation on cornmeal agar, providing a presumptive identification for laboratories lacking molecular diagnostic procedures.[65,66] A multiplex PCR assay was developed for rapid and accurate identification and differentiation of *L. elongisporus* from *C. parapsilosis* complex members among yeast isolates.[97]

Two other cases of *L. elongisporus* fungemia have been detected in recent years. The first case occurred in a 71-year-old female and despite therapy with caspofungin, the patient died on day 3 of her hospital stay (Table 1 and Supplemental Table S1).[66] The second case occurred in a premature, extremely low-birth-weight neonate, representing the first such case of its kind (Table 1 and Supplemental Table S1).[67] Again, only one dose of liposomal amphotericin B could be administered as the neonate expired due to sepsis on the same day when culture results became available.[67] In both cases, the isolates were identified as *C. parapsilosis* by Vitek 2 and as *L. elongisporus* by multiplex PCR and/or PCR-sequencing of rDNA (Table 1) and were susceptible to all antifungal drugs tested (Table 2). These reports[66,67] show that *L. elongisporus* is an emerging pathogen in Kuwait, particularly for patients in ICU settings with compromised/immature immune system, phenotypic methods alone may not be sufficient for accurate identification and rapid diagnosis may be crucial for improved outcome.

Fungemia cases due to M. capitatus*:*

Magnusiomyces capitatus (aka *Saprochaete capitatus*) and *Magnusiomyces clavatus* (aka *Saprochaete clavatus*) are emerging pathogens causing severe infections in patients with profound neutropenia with mortality rates ranging from 40% to 80%.[20,26] *Magnusiomyces* spp. are intrinsically resistant to fluconazole and echinocandins and so patients receiving fluconazole or echinocandin as prophylaxis or empiric treatment are prone to develop breakthrough infections.[23,126] A case of breakthrough invasive infection by *M. capitatus* also occurred in a young girl in Kuwait with relapsing acute myeloid leukemia during chemotherapy following bone-marrow transplantation.[68] The severely neutropenic patient was receiving broad-spectrum antibiotics for several episodes of bacteremia and caspofungin prophylaxis for 24 days. The blood samples as well as urine and tracheal secretions grew yeasts that were identified as *M. capitatus* by Vitek 2 and PCR-sequencing of rDNA (Table 1 and Supplemental Table S1). The cultured isolates showed reduced susceptibility to caspofungin (Table 2). Despite initiation of treatment with liposomal amphotericin B and removal of Port-A-Catheter, the patient expired on the third day.[68]

Two other cases of *M. capitatus* fungemia occurred in 2018 including breakthrough infection in one patient and both patients died before definitive diagnosis could be made (Table 1 and Supplemental Table S1).[69] The cultured isolates from both patients showed reduced susceptibility to fluconazole and resistance to echinocandins (Table 2). Thus, all three *M. capitaus* fungemia cases in Kuwait expired, which is consistent with very high mortality rates for invasive infections by this yeast.[20,26] Interestingly, Gram-stained smear of the cultured isolates showed numerous arthroconidia fragmenting into rectangular forms. This characteristic could be used for the presumptive identification of the yeast as *M. capitatus* pending confirmation by Vitek 2 and/or by PCR-sequencing of rDNA for rapidly initiating antifungal treatment with amphotericin B.[69]

Fungemia cases due to K. ohmeri*:*

Kodamaea ohmeri (aka *Pichia ohmeri*) is frequently mistaken for *Candida* as they both belong to Saccharomycetales.[22] This yeast has been isolated from various environmental sources, such as sand, seawater, swimming pools, and fruits and as a colonizer from the oral cavity of cancer patients.[127,128] *K. ohmeri* is an emerging human pathogen that causes life-threatening infections in critically ill immunocompromised patients requiring invasive monitoring and intervention with high mortality rates in fungemia cases.[22,23,127] The first case of persistent *K. ohmeri* fungemia occurred in a premature, low-birth-weight neonate (Table 1 and Supplemental Table S1).[70] The AST data showed higher MICs for fluconazole

but the isolates appeared susceptible to other antifungal drugs tested (Table 2). She was treated with amphotericin B for a total of 28 days with favorable outcome (Supplemental Table S1).[70]

The second *K. ohmeri* invasive infection was detected in 2018 in a 79-year-old patient (Table 1 and Supplemental Table S1). The isolate was resistant *in vitro* to fluconazole but appeared susceptible to voriconazole, caspofungin, and amphotericin B (Table 2). Although the underlying condition, comorbidities and other clinical details were not available, no specific antifungal treatment could be given as the patient expired within 2 days of investigations and before the culture results became available.[19]

Fungemia cases due to Rhodotorula *spp.:*

Rhodotorula spp. are environmental yeasts in Asia, contaminate surgical wound site, and are the causative agents in nearly 5% of non-*Candida* yeast invasive infections in China.[129] *Rhodotorula* spp., particularly *R. mucilaginosa* isolates, usually have higher MICs for azoles and echinocandins limiting therapeutic options to amphotericin B and 5-flucytosine.[47] A case of persistent catheter-related *R. mucilaginosa* fungemia was detected in a 4-year-old female with acute lymphocytic leukemia (Table 1 and Supplemental Table S1).[71] The patient had an episode of bacteremia prior to fungemia and the yeast was identified as *R. glutinis* by Vitek 2 and as *R. mucilaginosa* by PCR-sequencing of rDNA. In the absence of AST data, treatment was initiated with voriconazole instead of amphotericin B due to concerns for nephrotoxicity. After 3 weeks of therapy, the patient improved and was discharged from the hospital. However, the patient relapsed and was readmitted in the hospital and blood culture again yielded *R. mucilaginosa*. *R. mucilaginosa* DNA was detected in blood and the yeast was also isolated from the tip of Hickman catheter. The AST data showed higher MICs against fluconazole, voriconazole, posaconazole, and caspofungin (Table 2). Despite a higher MIC against voriconazole, treatment was again initiated by voriconazole. With the removal of catheter and continued treatment with voriconazole, the patient improved and subsequent blood cultures became negative.[71] A fungemia case due to another species (*R. minuta*) was also detected in 2018 by PCR-sequencing of rDNA. However, the clinical details, treatment given and outcome were not available.[19]

M. pachydermatis *fungemia*

Malassezia spp. are lipid-dependent yeasts and colonize the skin and mucous membranes of humans and animals. Systemic infections, reported at increasing frequency in recent years, are mainly caused by three species viz. *M. furfur*, *M. pachydermatis*, and *M. symphodialis*.[130] The risk factors for invasive infections include immature/severely compromised immunity, total parenteral nutrition, break in skin integrity, and invasive surgical procedures.[20,130] The first case of *M. pachydermatis* fungemia was detected in Kuwait in a preterm VLBW neonate.[72] The neonate received broad-spectrum antibiotics for multiple episodes of bacteremia before developing fungemia (Table 1 and Supplemental Table S1). The blood culture isolate was identified as *M. pachydermatis* by Vitek MS and PCR-sequencing of rDNA and was resistant, *in vitro*, to fluconazole, caspofungin, and 5-flucytosine (Table 2).[72] The patient was successfully treated with liposomal amphotericin B (Supplemental Table S1).[72]

P. laurentii *fungemia*

Papiliotrema laurentii (aka *Cryptococcus laurentii*) is an environmental yeast-like organism that was considered as a nonpathogenic species for humans with a normal immune system until recently. However, several invasive cases including fungemia and meningitis attributed to *P. laurentii* have been described in recent years.[131–133] An invasive infection caused by *P. laurentii* also occurred in a premature, VLBW female neonate in Kuwait (Table 1 and Supplemental Table S1).[73] Repeated blood cultures were identified as *P. laurentii* by Vitek 2, Vitek MS, and PCR-sequencing of rDNA and showed susceptibility to fluconazole, voriconazole, and amphotericin B but resistance to caspofungin (Table 2). Treatment was started with AmBisome. As the patient also developed bacteremia due to *Klebsiella pneumonia* during the course of antifungal treatment, combination therapy with broad-spectrum antibiotics, and AmBisome resolved the infection.[73]

Invasive infections by *Trichosporon* spp. have also been detected in Kuwait. *Trichosporon* spp. are yeast-like organisms that typically cause superficial infections (white piedra), allergic pneumonitis but can also cause invasive infections including fungemia.[23,134,135] *Trichosporonosis* is an emerging infection of severely immunocompromised patients and is mainly caused by *T. asahii*. Invasive

infections including bloodstream infections by *T. asahii* and *T. asteroides* have previously been detected in Kuwait; however, clinical details, treatment given, and outcome were not available.[136]

The increasing incidence of invasive infections by *Candida*/yeast species due to increasing number of at-risk (seriously ill, immunocompromised and premature, low-birth-weight neonates) patients presents considerable diagnostic and management challenges for treating physicians due to lack of specific signs and symptoms.[22–24,137] Early diagnosis, accurate AST, and early initiation of treatment with appropriate antifungal drugs form the cornerstone of effective management.[47–50,93,137] Diagnosing invasive infections by rare *Candida*/yeast species is even more challenging due to the inability of conventional diagnostic methods to identify these organisms accurately.[22,47] Although molecular methods are now regarded as the gold standard for definitive diagnosis, recent advances in phenotypic approaches have also been made that include expanding databases of yeast identification methods such as Vitek 2 and Vitek MS to identify many rare *Candida*/yeast species.[43–45,47,50] Chromogenic media and unique microscopic features could provide presumptive diagnosis of some rare yeast infections for resource-limited settings.[46,56,64,65,69] Imaging and biomarker-driven approaches may also help in early diagnosis.[47,116,137] Other novel approaches such as detection of fungal volatiles in breath-based biomarker tests are also being developed for the diagnosis of invasive *Candida*/yeast infections.[138] Treating physicians should consider the possibility of invasive *Candida*/yeast infections in patients with underlying medical conditions and other major risk factors who are not responding to adequate treatment with broad-spectrum antibiotics.

Although only four classes of antifungal drugs are currently available, combination therapy could be used to effectively manage the problem of intrinsic or developing drug resistance to reduce the high mortality rates associated with rare *Candida*/yeast invasive infections.[139] This approach has already been used successfully in some cases in Kuwait.[59,62,64,103] Another recent development that may help to improve the outcome of rare yeast infections is the growing pipeline of new antifungal drugs to augment the current antifungal armamentarium.

New antifungal drugs in the pipeline

Echinocandins, regarded as the first-line therapy for invasive *Candida*/yeast infections in adult populations, may not be so effective in neonatal population and the guidelines and recommendations for the total duration of therapy are also not well defined.[140,141] Some antifungal drugs affecting novel targets or improved pharmacological parameters have been developed and have shown promising results in phase II and phase III clinical trials involving patients with invasive *Candida*/yeast infections. A brief account of the new antifungal drugs in various stages of development is provided below.

In March 2023, the US Food and Drug Administration approved rezafungin, a novel echinocandin with increased half-life (133 h), which allows weekly dosing compared to daily administration for existing echinocandins, for the treatment of invasive *Candida*/yeast infections in ⩾18-year-old patients with limited or no alternative options.[142–145] Once-weekly dosing also makes rezafungin an attractive alternative for prophylactic or empiric treatment of hematological patients. A phase III randomized, double-blind trial (ReSTORE) has shown that once-weekly rezafungin is as effective as daily therapy with caspofungin followed by oral fluconazole. Nearly comparable occurrence of adverse events were seen in both groups of patients with invasive *Candida* infections.[146] Other studies to evaluate its role in antifungal prophylaxis as well as its safety, tolerability, and pharmacokinetics are also planned or are already being carried out.[147]

Ibrexafungerp is an oral and intravenous triterpenoid drug with broad activity against *Candida* spp., including azole-resistant organisms such as *C. auris* and echinocandin-resistant isolates.[144,148–150] The mechanism of action of ibrexafungerp is similar to echinocandins as it also inhibits 1,3-β-D-glucan synthase involved in the synthesis of the fungal cell wall but binds differently than echinocandins and so cross-resistance is limited.[151] Similar to echinocandins, it also has fungicidal activity against various *Candida* spp. including *C. auris* and *C. auris* isolates with *fks* mutations.[152] In a phase II clinical trial, it showed efficacy and safety comparable with standard of care treatment following initial echinocandin therapy. An oral dose of 750 mg/day was well-tolerated and achieved overall response rate comparable to that obtained with standard of care

treatment.[153] In a recent phase I trial, it demonstrated a favorable safety, tolerability, and pharmacokinetic profile.[154] Fosmanogepix, a guanosine monophosphate inhibitor targeting the enzyme Gwt1, has broad-spectrum activity against most *Candida*/yeasts and can be formulated for twice daily oral or intravenous administration.[144,150] In phase II clinical trials, it has shown clinical safety with no treatment-related serious adverse events and good efficacy.[155,156] It also shows excellent activity against *C. auris*.[155]

Other novel antifungal drugs are also in the pipeline. The ATI-2307 is a mitochondrial inhibitor that has shown activity against most *Candida* spp. isolates and also has the potential for the treatment of infections by drug-resistant organisms.[150,157,158] Several other drugs such as GR-2397, oteseconazole, opelconazole, and MAT2203 are also in various stages of clinical development.[142,148] These novel antifungals have the potential for expanding the choice of drugs available to improve the management of patients with invasive *Candida*/yeast infections.

Limitations of review

A limitation of our study is that only previously documented and published cases of invasive rare *Candida*/yeast infections in Kuwait are reviewed here. Thus, it is possible that some rare *Candida*/yeast invasive infections in Kuwait may have been missed, which is also a universal problem as diagnosis and treatment of these infections is extremely challenging. Also, the clinical details, treatment given, and outcome were not available for some of the patients described in the studies reviewed here, which may also have affected the epidemiology and outcome of rare *Candida*/yeast infections in Kuwait.

Conclusion

Considerable improvements were made in the diagnostic services offered to various hospitals of the Ministry of Health in Kuwait by the mycology laboratory in the Department of Microbiology, Faculty of Medicine, Kuwait University. Both traditional and molecular approaches were used for rapid diagnosis of invasive infections by common and rare fungal pathogens and their susceptibility or resistance to antifungal drugs. These advances resulted in the identification of 60 cases of fungemia or other invasive infections due to rare *Candida*/yeasts from Kuwait that were published as case reports or case series. Majority of these infections occurred among neonates ($n = 34$) followed by adult patients ($n = 19$), while the remaining seven cases occurred in pediatric patients. The clinical details, treatment given, and outcome were available for 28 of 34 neonates. All 28 were preterm, low/VLBW neonates receiving broad-spectrum antibiotics for one or more suspected or confirmed episodes of bacteremia in the NICU with many other risk factors for IFIs. The crude mortality rate among these neonates was 32.2% as 19 of 28 (67.8%) survived the infection and were discharged in healthy condition. The neonates were treated with amphotericin B or liposomal amphotericin B alone in nine cases, with liposomal amphotericin B plus azole or caspofungin in nine cases, and with liposomal amphotericin B followed by other antifungals either alone or in combination in six cases. One neonate was treated with fluconazole alone. One neonate died before culture results became available and specific treatment could be initiated while another one expired after only one dose of liposomal amphotericin B was administered. The mortality rate was higher among adult patients. Excluding 8 patients who either did not receive any treatment or only one dose of antifungal drug was administered as they expired before culture results became available, 11 patients received treatment, and 5 died with a crud mortality rate of 45.5%. It is expected that studies such as those reviewed here on the epidemiology of rare *Candida*/yeast invasive infections in different geographical regions, their susceptibility profiles, and management will help to formulate guidelines for improved patient outcome.

Declarations

Ethics approval and consent to participate

Not applicable as this is a review article based on studies previously published.

Consent for publication

Not applicable.

Author contributions

Suhail Ahmad: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Validation; Writing – original draft; Writing – review & editing.

Mohammad Asadzadeh: Data curation; Formal analysis; Validation; Writing – original draft; Writing – review & editing.

Noura Al-Sweih: Data curation; Formal analysis; Validation; Writing – original draft; Writing – review & editing.

Ziauddin Khan: Conceptualization; Data curation; Validation; Writing – original draft; Writing – review & editing.

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ORCID iD
Suhail Ahmad https://orcid.org/0000-0003-3492-4781

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