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CLINICAL MICROBIOLOGY - REVIEW

Update on invasive fungal infections in the Middle Eastern and North African region

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Abstract
In the recent years, the epidemiology of invasive fungal infections (IFIs) has changed worldwide. This is remarkably noticed with the significant increase in high-risk populations. Although surveillance of such infections is essential, data in the Middle Eastern and North African (MENA) region remain scarce. In this paper, we reviewed the existing data on the epidemiology of different IFIs in the MENA region. Epidemiological surveillance is crucial to guide optimal healthcare practices. This study can help to guide appropriate interventions and to implement antimicrobial stewardship and infection prevention and control programs in countries.

Keywords Invasive fungal infections · Invasive candidiasis · Invasive aspergillosis · *Pneumocystis* pneumonia · Cryptococcal meningitis · Mucormycosis · Histoplasmosis

Introduction

Invasive fungal infections (IFIs) have turned out to be a major public health concern along with the expansion of at-risk populations besides the lack of universal implementation of definitive diagnostics [1]. Numerous major risk factors for IFIs have been described including surgery, total parenteral nutrition, fungal colonization, renal replacement therapy, hemodialysis, mechanical ventilation, diabetes mellitus (DM), broad-spectrum antibiotics use, red blood cells transfusion, antifungal medication, central venous catheter, and peripheral catheter use [2]. In fact, IFIs can be divided into two categories: endemic mycoses like histoplasmosis and opportunistic mycoses like invasive candidiasis (IC), invasive aspergillosis (IA), cryptococcal meningitis (CM), *Pneumocystis jirovecii* pneumonia (PJP) [3].

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In liver transplant recipients, *Pneumocystis* is the underlying pathogen in 7% of all pneumonia cases [4]. The European Organization for Research and Treatment of Cancer (EORTC) in a cohort study has indicated that fungemia ranged from 0.15% in patients with solid tumors to 1.55% in hematopoietic stem cell transplantation recipients. It occurred predominantly due to *Candida* spp. infections (90%), where *C. albicans* (46.5%), and non-*albicans Candida* (NAC) (53.5%) were found in patients [5]. IFIs are an important cause of morbidity and mortality among high-risk groups including solid organ transplantation (SOT) recipients and hematological malignancy patients. For instance, mortality rates were the highest for IA (67–82%) as well as cerebral forms of mucormycosis (73.5%) [6].

Even though there are limited choices of antifungals, treating patients with confirmed fungal disease with effective antifungal agents is crucial to reduce morbidity and mortality. Also, several investigations described a significant link between early reliable diagnosis and treatment of IFIs and improved outcomes of patients at risk [7]. The diagnostic includes traditional methods like culture, histopathology, and imaging expertise and newer antigen- and PCR-based diagnostic assays [8].

In this review, we focus on the epidemiology, burden and incidences of IFIs in the Middle Eastern and North African (MENA) region among high-risk groups, to support infectious disease specialists and healthcare workers in this geographic area and assist the provision of optimal care for patients susceptible to IFIs.

Epidemiology of invasive fungal infections in the MENA region

Since the increase of IFIs is strongly associated with the expanding immunosuppressed population and the increase in invasive diagnostics and treatment, an urgent need for surveillance of the changing trends in incidences is required. The knowledge of the current situation allows the assessment of the burden of such infections in the region. Thus, PubMed, Science Direct, Scopus, and Google Scholar databases search was done for epidemiological studies of IFIs from tertiary care hospitals published in the last decade. We used a combination of the keywords for paper retrieving including the following: "invasive fungal infections," "invasive fungal disease," "invasive candidiasis," "candidaemia," "invasive aspergillosis," "pneumocystis pneumonia," "mucormycosis," "histoplasmosis," in addition to a MENA country. Indexed original articles and case reports in English and French of any design and sampling strategy were included. Despite the globally growing importance of invasive infections, especially among the high susceptible risk groups, the epidemiological assessment of the status of IFIs is underestimated in the MENA region. Indeed, only very few reports about the estimation of IFIs were found in this region in the last decade. In the next parts of this review, we will discuss the available data concerning IC, IA, CM, *Pneumocystis* pneumonia, mucormycosis, and histoplasmosis in the region.

Invasive candidiasis

Candida infections accounts for approximately 70 to 90% of total IFIs [9]. Global estimates indicated that ~ 750,000 cases of IC occur annually [10]. Candidemia (*Candida* bloodstream infection) is the most common clinical presentation of IC and occurs mainly in hospitalized patients with an ascribable mortality of 15–35% for adults and 10–15% for neonates [11]. Only five species contribute to almost 92% of cases of candidemia: *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*. *C. albicans* is the most common etiological agent worldwide [11]. However, an upward trend in the incidence of NAC in IC cases was witnessed worldwide, which may be correlated with an increasing use of triazoles, mainly fluconazole [12]. Furthermore, a recent emerging multi-drug resistant *Candida* species, *Candida auris*, has been reported to cause healthcare-associated fungal infections [13]. In comparison with *Candida* species, several characteristics make the opportunistic *C. auris* unique in the field of clinical mycology such as his ability to colonize inert surfaces, capacity to cause nosocomial invasive infections, resistance to some commonly used chlorine-based disinfectants, and non-susceptibility to any or all of the systemic antifungal drugs available at this time [14, 15].

Epidemiological studies assessing the status of IC, including candidemia, are underestimated in the developing world, counting MENA countries (Table 1). Several studies have estimated the incidence rates of candidemia in MENA countries. Candidemia incidence rate was estimated to be the highest in Qatar, with an estimated rate of (15.4/100,000) [16] and the lowest in Iran (0.34/100,000) [17] (Fig. 1). IC and other IFIs were compared with reported estimations in different countries at global level (Fig. 2).

As for the available epidemiological studies, only a few were found to assess the status of IC and candidemia. In Lebanon, only one study took place in the past 10 years. The study evaluating 2011–2012 data of three hospitals, with a mean of 2.2–2.5 co-morbid conditions per patient, has reported the incidence of IC to be 0.39 cases per 1000 hospital discharges [39]. In Jordan, an overall incidence rate of 0.48 episodes/1000 admissions was recorded in an academic tertiary hospital, with a 30-day mortality rate of 38.7% [40]. In Turkey, several studies have shown that nosocomial IC, including candidemia, ranged between 1.2/1000 and 5.6/1000 admissions [41–43]. The incidence of candidemia in ICUs ranged from 1.76 patients/1000 ICU admissions to 11.5 per 1000 neonatal ICU admissions among neonates [44, 45]. However, a prospective study in Iran indicated higher incidence rate of candidemia (15.2/1000 in neonatal ICU admissions), with a 42.5% mortality rate [46]. A systematic review and meta-analysis identified 55 cases of candidemia in Iran where the risk factors were surgery and burns (23.6%), malignancies (20%), use of broad-spectrum antibiotics (18.2%), and diabetes (7.3%) [47].

As for the Arabian Peninsula, it has been recorded in Saudi Arabia that IC rates ranged from 1.55–1.65 cases per 1000 discharges to 26 cases per 1000 ICU admissions [39, 48, 49]. A retrospective study on IC among pediatric patients indicated a group of risk factors: prematurity in 37 (28.7%) of patients, low birth weight (32.6%), central venous catheter (45.7%), malignancy (16.3%), immunotherapy (15.5%), and ventilator support (46.5%) [50]. In 2002–2009, data indicated that malignancy was independently associated with the development of candidemia [51]. In Kuwait, candidemia rate has decreased to a 0.15 cases/1000 in 2016 compared to 0.24 cases/1000 patient-days in 2014 [52]. In Qatar, 201 episodes of candidemia in 187 patients were identified in a single-center study [53].

In North Africa, candidemia in a pediatric ICU reached up to 3 per 1000 inpatient-days in Egypt [54]. A 15-year (1995–2009) retrospective analysis in the Sousse Region, Tunisia, had indicated an increase in the frequency of IC episodes, with an average of 24 episodes per year [55]. A previous study analyzing the data from 1995 to 2010 in the same region has shown an incidence of neonatal IC about 12.2 cases/1000

Table 1 Epidemiology of invasive candidiasis in the MENA region

Country	Clinical presentation	Study period	Incidence	Age of patients	Number of isolates	Predisposing condition	Causative agent	Sample type	Diagnostic tools	Mortality rate related to IFIs	Ref.
Lebanon and KSA	–	2011–2012	0.39 cases/1000 discharges (Lebanon) 1.21 cases/1000 discharges (KSA)	55.2 ± 25.1 y	102 with IFIs	Diabetes (41%) Coronary artery disease (24%) Leukemia (19%) Moderate to severe renal disease (16%) Congestive heart failure and chronic pulmonary disease (15%)	*C. albicans* (56%) *C. tropicalis* (20%) *C. glabrata* (14%)	–	Culture Chest radiograph CT Galactomannan PCR	33%	[39]
KSA	Candidemia (107 patients)	August 2012 and May 2016	26 cases per 1000 ICU admissions	58.4 ± 18.9 y	162	Diabetes (66%) (insulin treated* 29.6%) Chronic kidney disease requiring hemodialysis (34.2%) Active cancer (13.2%) Recent neutropenia (17%) Recent surgery (10.6%) Total parenteral nutrition (10.6%) Recent antibacterial therapy* (36.4%) Recent antifungal therapy* (11.9%)	*C. albicans* (38.3%) *C. tropicalis* (16.7%) *C. glabrata* (16%) *C. parapsilosis* (13.6%)	–	Culture	58.6%	[49]
KSA	–	January 2010 and January 2015	–	2.4 ± 1.41 y	129	ICU stay (62%) Antibiotics (65.9%) Prematurity (28.7%) Low birth weight (32.6%) Central venous catheter (45.7%) CVC (45.7%) Dialysis (8.5%) Malignancy (16.3%)	*C. albicans* (45.7%) *C. tropicalis* (21.7%) *C. parapsilosis* (12.4%) *C. famata* (5.4%) *C. lusitaniae* (3.9%) Others (10.9%)	Blood CSF Sterile body fluids (synovial fluid, peritoneal fluid, and pleural fluid)	–	Ventilator-related* (48.3%) ICU-related* (43.8%)	[50]

Table 1 (continued)

Country	Clinical presentation	Study period	Incidence	Age of patients	Number of isolates	Predisposing condition	Causative agent	Sample type	Diagnostic tools	Mortality rate related to IFIs	Ref.
						Neutropenia (18.6%) Immunodeficiency (10.1%) Immunotherapy (15.5%) Previous antifungal (24.8%) Recent steroid (14.7%) Ventilator support (46.5%)					
KSA	Candidemia	2002–2009	–	< 1 to > 60 y	258	Malignancy* Use of corticosteroids ICU admission Antibiotics and antifungals use Prior major surgery Neutropenia Diabetes mellitus Long-term dialysis* Organ transplantation	*C. albicans* (34.1%) *C. tropicalis* (15.5%) *C. parapsilosis* (11.9%) *C. glabrata* (9.1%) *C. famata* (4.4%) *C. krusei* (4%) *C. guilliermondii* (2%) *C. lusitaniae* (0.8%) *C. zeylanoides* (0.4%)	Blood	Culture Biochemical identification	–	[51]
KSA	–	January 2003 to December 2012	1.65 per 1000 hospital discharges per year	52 y	652	–	*C. albicans* (38.7%) *C. tropicalis* (18.9%) *C. glabrata* (16.3%) *C. parapsilosis* (12.6%)	Blood Cerebrospinal fluid Other body fluid Tissue biopsies	Culture Biochemical identification	40.6%	[48]
Jordan	Candidemia	–	0.48 episodes/1000 admissions	–	158	Central venous catheterization* Mechanical ventilation* ICU admission Broad antibiotics use	*C. albicans* (44.3%) NAC (42.2%)	–	–	38.7% (independent mortality risk factors*: mechanical ventilation, ICU admission,	[40]

Table 1 (continued)

Country	Clinical presentation	Study period	Incidence	Age of patients	Number of isolates	Predisposing condition	Causative agent	Sample type	Diagnostic tools	Mortality rate related to IFIs	Ref.
										length of stay, *C. albicans*, CVC, severe sepsis, and septic shock)	
Qatar	Candidemia	January 1, 2004 to December 31, 2010	–	< 1 to > 60 y* (65.8% males)	201	Malignancies (17% hematological and solid organ tumors) GI disease including surgery (13%) Renal diseases including transplant patients (11%)	*C. albicans* (33.8%) *C. glabrata* (18.9%) *C. tropicalis* (17.9%) *C. parapsilosis* (16.9%) *C. dubliniensis* (1.5%) *C. orthopsilosis* (4%) *M. guilliermondii* (1%)	Blood	Molecular identification Biochemical identification MALDI-TOF MS	Crude-mortality: 56.1% (Heart/pulmonary diseases-related (24%); Malignancies (hematological and solid organ tumors) (22.1%); GI (10.5%); Renal diseases (12.5%)	[53]
Kuwait	Candidemia	2014–2016	0.24 (2014), 0.16 (2015), and 0.15 (2016) cases/1000 patient-days	59–66 y	89	Diabetes ($n = 41$) Antimicrobial agent(s) prior to candidemia ($n = 74$) Vascular catheter (79%) Hemodialysis (12%) Total parenteral nutrition (15%) Abdominal surgery (20%) ICU admission (20%)	*C. albicans* (32%) *C. parapsilosis* (32%) *C. tropicalis* (20%) *C. glabrata* (13%) *C. dubliniensis* (1%) *C. famata* (1%) *C. auris* (1%)	–	–	54% (related factors: ICU stay*, *C. tropicalis**, abdominal surgery*)	[52]
Turkey	Candidemia	2010–2016	0.10 to 0.30 cases/1000 patient-days	45 y (55.1% males)	351	ICU admission (58.7%) Underlying malignancy (35.6%) Central venous line (81.5%) Parenteral nutrition (55.8%)	*C. albicans* (48.1%) *C. parapsilosis* (25.1%) *C. glabrata* (11.7%)	Blood	Culture	Total: 40.7% *C. albicans* (36.1%), and non-*albicans Candida* spp. (39.6%)	[135]

Table 1 (continued)

Country	Clinical presentation	Study period	Incidence	Age of patients	Number of isolates	Predisposing condition	Causative agent	Sample type	Diagnostic tools	Mortality rate related to IFIs	Ref.
						Major surgery (42.7%)					
Turkey	–	January 2000 and December 2007	11.5 per 1000 NICU admissions		28	Maternal pre-eclampsia Prematurity* Prolonged mechanical ventilation* Prolonged hospitalization* Prolonged total parenteral nutrition* Presence of jaundice. Retinopathy of prematurity Bronchopulmonary dysplasia	*C. parapsilosis* (57.1%) *C. albicans* (42.9%)	Blood	Culture	42.8%	[45]
Turkey	Nosocomial candide-mia	June 30, 2007 and June 30, 2009	–	1–54 y (51.0% males)	120	Pediatrics: Prematurity (25.5%) Neoplasia (17.6%) Infection (15.7%) Adults: Neoplasia (36.2%) Trauma (13.0%) Infection (17.4%)	*C. albicans* (43.3%) *C. parapsilosis* (25.0%) *C. tropicalis* (17.5%)	Blood	Culture	–	[136]
Iran	Candidemia	November 2016 to August 2017	–	48 ± 16.6 y (40% males)	5 (6.25-%)	AML (80%) Central venous catheter (100%)	*Candida* spp.	Blood	Culture	–	[137]
Iran	Candidemia	–	–	46.80 ± 24.30 y	55	Surgery* and burns (23.6%) Malignancies (20%) Broad-spectrum antibiotic use (18.2%) Diabetes (7.3%)	*C. parapsilosis* (30.8%) *C. albicans* (27.3%) *C. glabrata* (18.2%) *C. tropicalis* (14.5%)	–	–	–	[47]
Iran	Candidemia	May 2011–November 2013	–	48.2 ± 30.9 y (40% males)	–	Cancer (20%) Diabetes (20%) Premature birth (20%)	*C. albicans* (50%) *C. glabrata* (40%)	Blood	Culture PCR	60%	[138]

Table 1 (continued)

Country	Clinical presentation	Study period	Incidence	Age of patients	Number of isolates	Predisposing condition	Causative agent	Sample type	Diagnostic tools	Mortality rate related to IFIs	Ref.
						Multiple trauma and vast surgery (40%) Surgery, dialysis, diabetes, or renal failure (20%)	*C. parapsilosis* (10%)				
Egypt	Candidemia	–	3 per 1000 inpatient--days	6 m–15 y (54.5% males)	88	Respiratory tract disease (15.2%) Neurological diseases (12.1%) Cardiovascular disease (9.1%) Nephropathy (4.5%) Endocrinopathy (3%) Chronic liver disease (1.5%)	*C. albicans* (40%) *C. parapsilosis* (25%) *C. tropicalis* (17%) *C. glabrata* (8%)	Blood	Culture	16.7%	[54]
Tunisia	–	1995 to 2010	12.2 cases/1000 admissions (average)	25–41 w	265	Broad-spectrum antibiotics (98.4%) Central catheter (68.3%)	*C. albicans* (74.3%) *C. parapsilosis* (13.6%) *C. glabrata* (4.5%) *C. tropicalis* (3.8%) *C. lusitaniae* (1.5%) *C. krusei* (0.7%) *C. guilliermondii* (0.4%) *C. pelliculosa* (0.4%) *C. ciferrii* (0.4%) *C. zeylanoides* 1 (0.4)	Blood (100) Central catheter (133) CSF (18) Peritoneal fluid (4) Hepatic abscess (4) Joint fluid (2) Intra-abdominal abscess (1) Mediastinal fluid (1)	–	63%	[56]
Tunisia	–	January 1995–December 2009	24 episodes per year (average)	–	369	–	*C. albicans* (64.0%) *C. parapsilosis* (13.3%) *C. tropicalis* (11.6%)	Normally sterile sites (blood, CSF, pleural, peritoneal, and joint fluids)	Culture Biochemical tests	–	[55]

Table 1 (continued)

Country	Clinical presentation	Study period	Incidence	Age of patients	Number of isolates	Predisposing condition	Causative agent	Sample type	Diagnostic tools	Mortality rate related to IFIs	Ref.
							C. glabrata (5.4%)	Biopsy specimens from deep organs			

C. albicans Candida albicans, *C. glabrata*, *Candida glabrata*, *C. parapsilosis Candida parapsilosis*, *C. tropicalis Candida tropicalis*, *C. guilliermondii Candida guilliermondii*, *C. pelliculosa Candida pelliculosa*, *C. ciferrii Candida ciferrii*, *C. zeylanoides Candida zeylanoides*, *C. lusitaniae Candida lusitaniae*, *C. famata Candida famata*, *C. auris Candida auris*; *IFIs* invasive fungal infections, *CSF* cerebrospinal fluid, *GI* gastrointestinal, *ICU* intensive care unit, *NICU* neonatal intensive care unit, *AML* acute myeloid leukemia, *GI* Gastrointestinal, *MALDI-TOF MS* Matrix-assisted laser desorption ionization time-of-flight mass spectrometry, *PCR* polymerase chain reaction, *CSF* cerebrospinal fluid, *CT* computerized tomography, *CVC* central venous catheter, *y* years, *m* months, *w* weeks, *KSA* Kingdom of Saudi Arabia

*Significant association ($p < 0.05$)

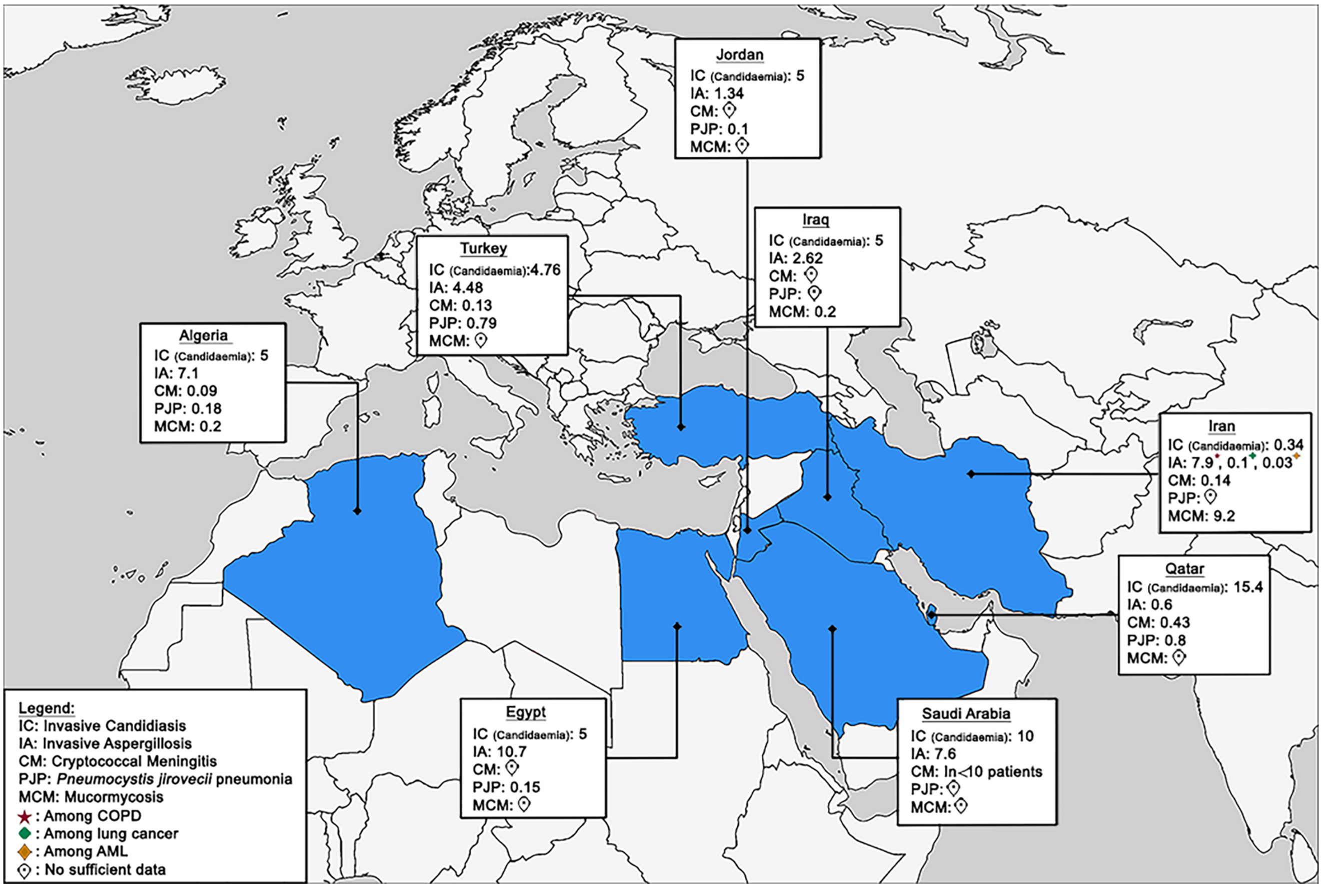

Fig. 1 Available estimates of the incidence rate (per 100,000 population) of invasive fungal infections in MENA countries [16–22]

admissions, with a fourfold decrease of incidence from 2007 to 2010 [56]. A retrospective study of IFI among renal transplant recipients from January 1995 to February 2013 reported only 2 cases of IC [57]. In Morocco, 8-month prospective surveillance from January to August 2011 conducted at the Casablanca University Hospital—pediatric hematology/oncology unit—showed a healthcare-associated infections (HAIs) incidence of 28/1000 patient-days, where *Candida* accounted for 14% [58].

Some factors may have a probable role in the spread of IFIs among MENA countries. For instance, country socioeconomic status affects device-associated infection rates in developing countries and should be taken into account when comparing device-associated infections from one country to another [59]. In addition, the global share of the health research in the Eastern Mediterranean region is lower than the average percentage worldwide. The rise in academic health publications has been more common in only a few countries [60]. Furthermore, socio-political instabilities influence research output as well, such as in Egypt and Tunisia in the last few years. The concentration of biomedical and health research in the region's academic institutions is expected to help turn information into public health results, if more suitable conditions are given [60].

Based on data published in the last decade regarding IC causative agents, *C. albicans* was found to be the most prevalent in Iran (80%) in a local study conducted in Tehran, followed by Turkey (48.3%), Kuwait (37.22–47.2%), and Qatar (30.2%) [61, 62]. According to Ghazi et al. [62], an increase in NAC is being observed in the MENA region, especially in Saudi Arabia (48.1%), Kuwait (52.8%), Egypt (60%), Qatar (69.3%), and Tunisia (~ 76.1%). A decrease in the NAC incidence was observed in Turkey (from 52.43 to 44%). With regard to the NAC distribution, *C. tropicalis* was prevalent in Saudi Arabia (15.5%), and Tunisia (37.7%), while *C. glabrata* predominated in Qatar (25.5%), Turkey (13.3%), and Iran (20%) and *C. parapsilosis* in Kuwait (38.2%) and Egypt (25%) [62].

Concerning *C. auris*, it was associated with IC, mostly candidemia, in the United Arab Emirates, Kuwait, and Saudi Arabia [52, 63–68]. Surprisingly, while *C. auris* isolation in Kuwait has steadily increased over a study period and almost doubled in 2018 compared to 2017, a noteworthy finding of nearly sixfold increase was in bloodstream *C. auris* isolates in the same period [68]. Unfortunately, no reports of *C. auris* were found form other MENA countries. In fact, *C. auris* is closely related to the species of the *C. haemulonii* complex, leading to a misidentification with other *Candida* species such

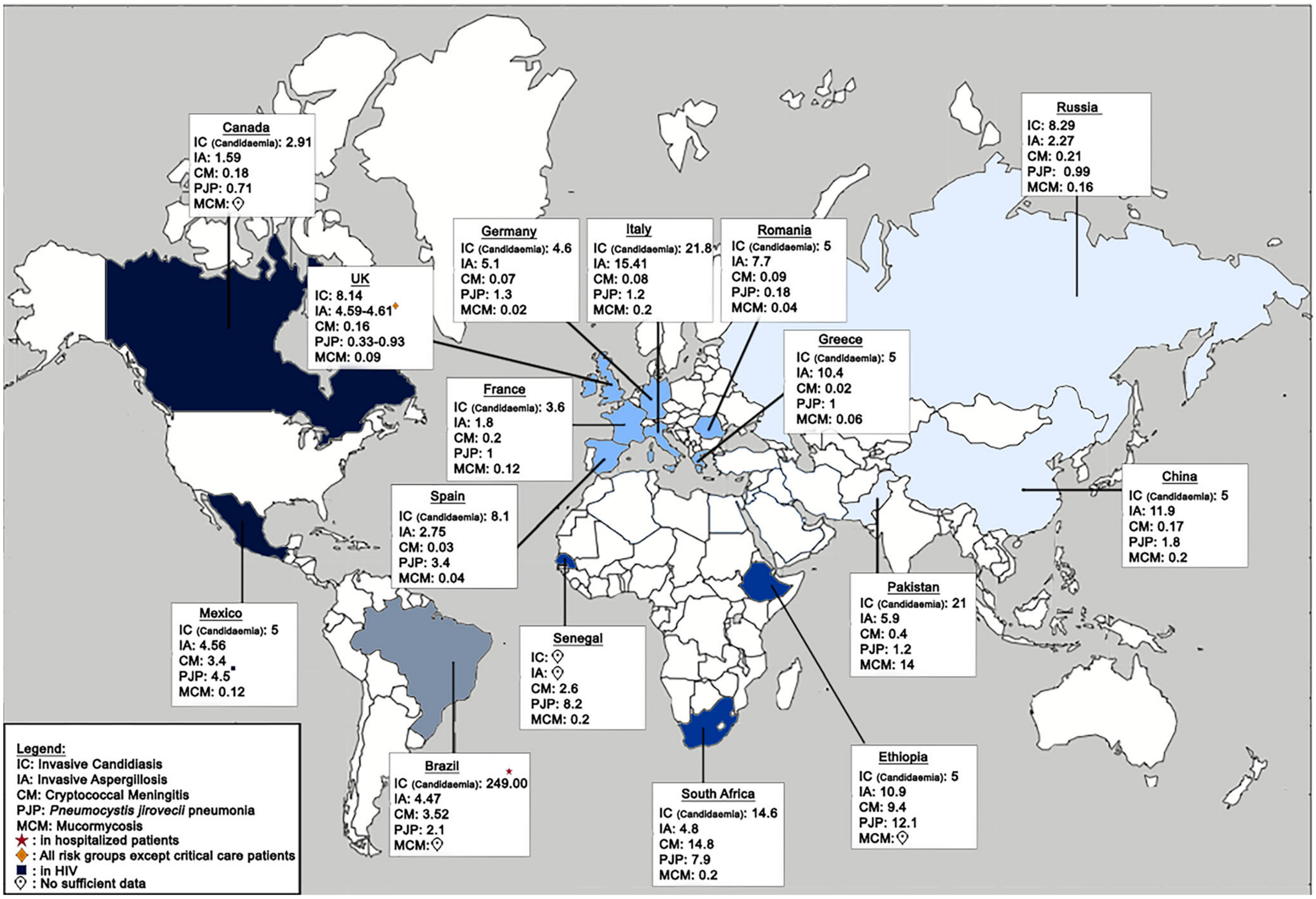

Fig. 2 Available estimates of the incidence rate (per 100,000 population) of invasive fungal infections in different countries around the world [23–38]

as *C. haemulonii* or *C. famata* [69, 70]. Even though most of the region belong to the middle-income countries, the total mass of the publication of research is lower than its global proportion of population or income [60]. Most of the clinical microbiology laboratories in this geographic area are not yet supported with more advanced diagnostic tools that allow the extensive search for this agent, in contrary to the high-income countries, which reported and investigated to a certain extent the *C. auris* distribution. *C. auris* infection may be present in other countries as well, but its occurrence has not yet been investigated. Unfortunately, the insufficiency of conventional commercial systems to identify *C. auris* also leads to delayed intervention and treatment [70, 71]. This will definitely cause a threat in the healthcare settings, since this fungal agent can contaminate and prevail in hospital environments, in addition to transfer between patients, and from health workers and abiotic surfaces of medical equipment to patients [72].

Invasive aspergillosis

IA is an opportunistic fungal infection affecting primarily the immunocompromised population: 70% of the total putative or proven IA happens in immunocompromised patients, in patients with chronic obstructive pulmonary disease (COPD), or patients with diabetes admitted to the ICUs [73]. It is estimated that ~250,000 cases occur annually [10]. IA is associated with elevated hospital mortality, extended duration of hospitalization, and high costs [74]. The causative agent *Aspergillus* spp. is a ubiquitous environmental mold that is found on organic matter, soil, and in the air as conidia [75]. *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus versicolor* are the most common causative species, where *A. fumigatus* is the commonest agent worldwide [76]. Despite the growing concern of aspergillosis, it is not thoroughly reported in the majority of MENA countries (Table 2).

IA burden estimates have been done for several MENA countries, and the highest estimated incidence rate in Egypt is 10.7/100,000 [18], followed by Iran with 7.9/100,000 among COPD cases, 0.1/100,000 among lung cancer cases, and 0.03/100,000 among acute myeloid leukemia cases [17]. In Saudi Arabia, incidence rate was 7.6/100,000 [19], followed by Algeria (7.1/100,000) [20], Turkey (4.48/100,000) [21], Iraq (2.62/100,000) [77], Jordan (1.34/100,000) [22], and reached its lowest value (0.6/100,000) in Qatar [16]. Moreover, the incidence of IA in Lebanon was estimated at 1.21 cases/1000 hospital discharges, higher than that found in Saudi Arabia with 0.4 cases/1000 hospital discharges [39]. In

Table 2 Epidemiology of invasive aspergillosis in the MENA region

Country	Study period	Setting	Incidence	Age of patients (% gender)	Number of isolates	Predisposing condition(s)	Causative agent	Sample type	Diagnostic tool	Mortality rate	Ref.
Lebanon and KSA	2011–2012	Five hospitals (3 in Lebanon and 2 in KSA)	1.21 cases/1000 discharges (Lebanon) 0.4 cases/1000 discharges (KSA)	55.2 ± 25.1 y (54.9% males)	102 with IFIs	Diabetes (41%) Coronary artery disease (24%) Leukemia (19%) Moderate to severe renal disease (16%) Congestive heart failure and chronic pulmonary disease (15%)	*A. fumigatus* (60%) *A. niger* (10%) *A. flavus* (10%).	–	Culture Chest radiograph CT Galactomannan PCR	IFIs-related (33%)	[39]
Bahrain	2009—2013	The Salmaniya Medical Complex	–	52.85 y	60	Diabetes (23%) COPD (17%) Malignancy (15%) SOT (2%) Corticosteroid therapy (23%) Radiotherapy/chemotherapy (12%) Immunosuppressive therapy (7%)	*A. fumigatus* (53%) *A. niger* (28%) *A. flavus* (12%) *Aspergillus* spp. (7%)	Sputum (50%) ETA (30%) BAL (20%)	Gram stain Direct sputum smear Culture Chest X-ray/CT	Colonized patients (25%) Probable cases (44%) Putative cases (32%)	[78]
Tunisia	December 2009 to November 2011	Farhat Hached Hospital	7.5%	1–65 y*	56	ALL AML	*A. niger* (35%) *A. flavus* (38%) *A. tubingensis* (19%) *A. fumigatus* (4%) *A. westerdijkiae* (2%) *A. ochraceus* (2%)	–	Microscopy MALDI-TOF MS PCR CT scan	–	[80]
Tunisia	December 2004–September 2007)	Hedi Chaker Hospital	15%	–	1680	AML ALL Neutropenia Medullar aplasia	*A. flavus* (79.2%) *A. niger* (10%) *A. ochraceus* (2.3%) *A. fumigatus* (2.3%)	BAL Effusion drainage Biopsies	Microscopy Galactomannan detection by ELISA PCR	–	[81]

A.fumigatus Apergillus fumigatus, *A. niger Aspergillus niger*, *A. flavus Aspergillus flavus*, *A. ochraceus Aspergillus ochraceus*, *A. westerdjikiae Aspergillus westerdjikiae*, *A. tubingensis Aspergillus tubingensis*, *AML* acute myeloid leukemia, *ALL* acute lymphocytic leukemia, *SOT* solid organ transplantation, *COPD* chronic obstructive pulmonary disease, *BAL* bronchoalveolar lavage, *CT* computerized tomography, *MALDI-TOF MS* matrix-assisted laser desorption ionization time-of-flight mass spectrometry, *ELISA* enzyme-linked immunosorbent assay, *PCR* polymerase chain reaction, *ETA* endotracheal aspiration, *IFIs* invasive fungal infections, *y* years, *KSA* Kingdom of Saudi Arabia

*Significant association ($p < 0.05$)

Bahrain, medical records during 2009–2013 of a tertiary care hospital of patients with positive *Aspergillus* cultures revealed 53.3% colonization and 46.7% presumed IA associated with 25% and 32% mortality respectively [78]. In Tunisia, the incidence of IA was 7.5–15% among hematology patients [79–81]. A retrospective study of IFIs among renal transplant recipients at Habib Bourguiba Sfax university hospital from January 1995 to February 2013 reported 2 cases of aspergillosis [57]. Between 2002 and 2010, 29 cases of IA were reported in the Sousse Farhat Hached Hospital Hematology Unit, where acute myeloid leukemia (AML) was the most common disease (65.5%) among the severely neutropenic patients [82].

Regarding species distribution, *A. fumigatus* predominated in IFIs of hospital discharges in both Lebanon and Saudi Arabia (60%) [39] and was responsible for 53% of IA in Bahrain [78]. *A. flavus* was predominant in 75% of bronchoalveolar lavage (BAL) samples in Iran [83] and in 37.5% of sputum samples and 79.2% among clinical samples of hematology patients in Tunisia [81, 84].

Cryptococcal meningitis

Cryptococcus neoformans is the most common fungal agent that causing meningoencephalitis in the immunocompromised individuals worldwide [85], followed by *Cryptococcus gatti* [86]. *C. neoformans* is acquired through inhalation of spores or dried agent in the environment [87]. CM arises in 15% of AIDS-related mortality worldwide [88]. It is estimated that ~ 223,100 incident cases occur globally, with an estimation of 181,100 annual deaths [88].

Considering CM as a rare fungal infection, it could not be estimated in Jordan [22], Iraq [77], and Egypt [18], in addition to being estimated to probably be affecting under 10 patients in Saudi Arabia [19]. In Qatar, CM had a low estimated incidence rate of 0.43 cases per 100,000 considering the low human immunodeficiency virus (HIV) rate in the country [16]. In Turkey, the estimated rate was 0.13 per 100,000 population with the prediction of 106 annual cases occurring among HIV patients [21]. Similarly, the incidence rate in Iran was estimated at 0.14 per 100,000 population [17]. In Algeria, a nearly negligible rate of 0.09 per 100,000 population was estimated [20].

Overall, few cases of CM were reported in the MENA region. A case was observed in a Turkish female who has undergone mastectomy and has had received chemotherapy following surgery [89]. In addition, a rare case of tenosynovitis caused by *Cryptococcus luteolus* was reported in a 68-year-old type 2 diabetic male [90]. Regarding Iran, a review article reported a case of CM caused by *C. neoformans* in HIV-positive Iranian female who died 4 days after antifungal therapy due to respiratory failure in Sari. The authors have also included 12 other reported cases of cryptococcosis due to *Cryptococcus* species between 1969 and 2014 [91]. Moreover, a study showed that the prevalence of cryptococcal infection in HIV-infected patients with a CD4 cell count of < 100 cells/mm^3 was very low (< 3%) [92]. In fact, *C. neoformans* is highly prevalent in pigeon droppings in Iran, allowing its transmission to the environment and consequently to the patients at risk of developing CM [93, 94].

The first report of CM in the Arabian Peninsula was in Saudi Arabia in 1990, showing the occurrence of this disease in a child having systemic lupus erythematosus [95]. The only reported case from Kuwait was in 1995, considered the second in the Arabian Peninsula, in a 22-year-old man presented with confusional psychosis caused by *C. neoformans* serotype A [96]. However, in Oman, a study conducted between January 1999 and December 2008 showed that CM accounted for 22% of AIDS-defining opportunistic infections [97].

Regarding the North African region, 0.6% of CM cases were estimated among annually HIV-infected patients in Egypt [18]. The first cases of CM were reported in two HIV-positive patients in Libya [98]. In Morocco, a study that was conducted from January 2005 to May 2015 showed that CM accounted for 20% of neurological disorders involved that was suggestive of HIV infection in 68.8% cases [99]. A 2016 cross-sectional study in Tunisia declared that CM was responsible for 11% out of 70.4% deaths associated with HIV [100]. Among renal transplant recipients between January 1995 to February 2013, 2 cases of cryptococcosis were reported [57].

Pneumocystis pneumonia

Pneumocystis spp., a ubiquitous yeast-like fungus that affects a wide variety of mammals, is a host strict agent where *P. jirovecii* infects primarily humans [101]. The main transmission route is through inhalation; however, some evidence suggests a direct-contact transmission route [102]. PJP is widely known as an HIV-positive-related opportunistic fungal infection. However, because of the extensive use of immunosuppressant drugs, non-HIV risk groups have emerged, particularly among cancer patients [103].

Concerning incidence rate estimates, it could not be estimated in both Iraq and Saudi Arabia due to the lack of data on PJP infections [19, 77]. In Qatar, the estimated rate was 0.8 per 100,000 population [16], followed by Turkey 0.79 per 100,000 [21], Algeria 0.18 per 100,000 [20], Egypt 0.15 per 100,000 [18], and Jordan 0.1 per 100,000 [22] (Table 3).

Case reports and epidemiological data on PJP were reported in few countries. A Lebanese report indicated a prevalence of 10.9% PJP cases among HIV patients [104]. In Turkey, the prevalence of PJP among AIDS/HIV patients ranged from 10 to 46.7% [104–106], while in Iran, PJP ranged from 4.5 to 39.3% [107–109]. Regarding the Arabian Peninsula region, PJP occurring in 9 episodes among primary immunodeficiency disorder patients in Kuwait [110] was found in 5.1% of

Table 3 Epidemiology of *Pneumocystis jirovecii* pneumonia in the MENA region

Country	Study period	Setting	Incidence	Age of patients	Number of isolates	Predisposing condition(s)	Sample type	Diagnostic tool	Mortality rate	Ref.
Lebanon	1984 to January 2008	American University of Beirut Medical Center	10.9%	35.4 y	89	HIV	–	–	–	[104]
Turkey	2009–2015	Ege University Hospital	–	56.7 ± 15.3 y	43	CMV co-infection	BAL, sputum and endotracheal aspiration	Microscopy Real-time PCR	PJP: 46.7% Co-infection: 78.6%	[105]
Turkey	1992–2009	Erciyes University Hospital Infectious Diseases Clinics	–	45 y	–	HIV/AIDS	–	–	–	[106]
Iran	2011	Imam Khomeini and army's 501 hospitals	39.3% (77.5% in AIDS group)	19–58 y	160	AIDS, diabetes, Hodgkin lymphoma, non-Hodgkin lymphoma	Serum	Indirect fluorescent antibody test	–	[107]
Iran	June 2010–December 2011	National Research Institute of Tuberculosis and Lung Disease (NRITLD)	10.5%	Age: 23–65	153	Malignancy under chemotherapy	BAL	Nested PCR	–	[108]
Iran	2000–2015	Imam Khomeini Hospital	4.5%	15–63 y	177	HIV/AIDS	–	–	–	[109]
Kuwait	January 2004 and December 2013	Kuwait National Primary Immunodeficiency Disorders Registry	8.3%	–	–	Primary immunodeficiency disorders	–	–	–	[110]
Bahrain	January 2009–May 2013	Salmaniya Medical Complex (SMC)	15.1%	48.3 ± 11.6 y	10	HIV-positive patients	BAL	Direct antigen detection test using an immunofluorescence method	–	[111]
Oman	January 1999 and December 2008	Sultan Qaboos University (SQU) Hospital	25%	37.5 y	19	HIV/AIDS	Sputum	Microscopy Radiography High-resolution CT	–	[97]
Libya	2013	Tripoli Medical Center	8.8%	40 y	227	HIV/AIDS	–	Clinical presentation chest X-ray/computerized tomography treatment response	37.4%	[112]
Tunisia	January 2000 and August 2014	Infectious Disease Services of Sousse and Monastir at the Tunisian Center	–	40 ± 11 y	213	HIV/AIDS	–	–	HIV-related: 70.4% (pulmonary pneumpocystosis (11%))	[100]

PJP *Pneumocystis jirovecii* pneumonia, *HIV* human immunodeficiency virus, *AIDS* acquired immunodeficiency syndrome, *PCR* polymerase chain reaction, *BAL* bronchoalveolar lavage, *CMV* cytomegalovirus, *CT* computerized tomography, *y* years total HIV-infected patients in Bahrain [111], while accounted for 25% of opportunistic infections in HIV/AIDS patients in Oman with no mortality reported due to this infection [97]. Concerning North Africa, a retrospective analysis in 2013 conducted on HIV-related hospitalizations showed that PJP was responsible for 8.8% respiratory diseases in Libya [112] and accounted for 11.1% death in HIV-infected patients in Tunisia [100]. Another retrospective study from January 1995 to February 2013 on IFIs reported 4 cases of pneumocystosis among renal transplant recipients [57].

Mucormycosis

Mucormycosis is an IFI ordinarily seen in individuals with underlying predisposing risk factors including DM and hematological malignancies. Disseminated forms are usually seen in individuals with such risk factors, although rhino-sinusoidal and cutaneous forms may occur in all individuals [113]. Causative agents belong to the subphylum Mucoromycotina. *Rhizopus arrhizus* is the most common agent causing mucormycosis globally. It is acquired through inhalation of sporangiospores [114]. The global estimates of mucormycosis were around > 10,000, with an estimate of disseminated mucormycosis around 100,000 [10].

Estimated incidence rates were scarce. The highest estimated rate was in Iran at 9.2 per 100,000 population [17], then in Iraq and Algeria at 0.2 per 100,000 [20, 77]. In Lebanon, an average incidence of 0.83 cases/10,000 admissions (range 0–2.22) was seen over a 10-year period in hospitalized patients, in addition to 20% mucormycosis-related deaths [115]. As for Turkey, 223 cases occurred in hematological malignancies patients and 214 cases in patients with diabetic ketoacidosis [21]. A 17-year assessment indicated 60% cases of rhino-cerebral and 1.9% disseminated forms of mucromycosis diagnosed in 151 patients, with 49% diabetes 39.7% hematological malignancies comorbidities among them [116]. In Iran, a systematic review indicated that the commonest form was rhino-cerebral (48.9%) in addition to eight disseminated forms were identified which accounted for 75% of total mortality [117]. Another 10-year assessment indicated the prevalence of the rhino-cerebral form (95%) among the total diagnosed mucormycoses [118]. In addition, a case of rhino-orbital mucormycosis caused by *Rhizopus oryzae* was reported in an acute lymphoblastic leukemia patient [119]. Among children with hematological malignancies, mucoromycetes were responsible for 11.5% of IFIs and accounted for 53.3% mortality [120]. An overall incidence rate was estimated at 4.27 per 100 leukemia patients, which decreased from 2001 to 2011 [121].

Concerning the Arabian Peninsula, mucormycosis was estimated to probably being affecting less than 10 patients in Saudi Arabia [19]. A retrospective analysis has reported rhino-cerebral mucormycosis as a cerebral venous thrombosis (CVT) [122]. Gangrenous necrotizing cutaneous mucormycosis in a female neonate who has had injuries on the scalp, abdomen, and back was reported in an ICU in Oman [123].

In North Africa, proven mucormycosis developed in 45 patients in which 90% of the cases had hematological malignancies in Egypt; in addition to mucormycosis-related complications in 5 cases with disfigurement and perforated hard palate. Mucormycosis-related mortality was 33% [124]. In December 2010, 3 out of 5 acute leukemia patients due to *Rhizomucor* outbreak [125]. Another study during 2010 reported 10 cases of mucormycosis, in which 80% had pulmonary mucormycosis and only 20% sinus involvement [126]. As for Tunisia, two patients had died after reporting rhino-cerebral, rhino-orbital, auricular, pulmonary, and cutaneous mucormycosis in one acute leukemia and 3 diabetic patients. The responsible Mucorales were *R. arrhizus* in 3 cases and *Lichtheimia corymbifera* in 2 cases. [127]. One mucormycosis was reported among 321 renal transplant recipients [57]. Surprisingly, considering the rarity of hemophagocytic lymphohistiocytosis, it was reported to be complicated by sinonasal mucormycosis in a diabetic child [128]. Retrospective analysis of data between 1992 and 2007 included 17 diabetic patients with rhino-orbito-cerebral mucormycosis which resulted in 65% mortality primarily due to delay in diagnosis and the lack of surgical treatment [129] (Table 4).

Histoplasmosis

Histoplasma capsulatum, a dimorphic fungus and causative agent of human histoplasmosis, causes respiratory and systemic mycoses in immunocompromised individuals [130]. The global burden of disseminated histoplasmosis is estimated to be ~ 100,000 annual cases [10]. The co-occurrence of histoplasmosis and tuberculosis in advanced HIV poses a diagnostic problem especially in histoplasmosis endemic regions [131]. Histoplasmosis is a known endemic mycoses of North America [132]; however, some reports were made from North Africa. In Morocco, a 39-year-old HIV-infected patient presented sinusitis and cutaneous histoplasmosis [133]. As well, a case of disseminated histoplasmosis caused by *H. capsulatum* was diagnosed in the bone marrow of a 34-year-old HIV-infected woman at Rabta Hospital of Tunis [134].

Concluding remarks

Despite the limited number of investigations dealing with the epidemiology of IFIs in this geographic area, the currently available data underlines that IFIs are not negligible. There is an urgent need for surveillance and implementation of recommendations and procedures in tertiary care centers in order to stem the morbidity and mortality related to IFIs, particularly among high-risk populations. Furthermore, a regional reference center for invasive mycoses and antifungals at the MENA region, with broad missions, is needed to promote

Table 4 Epidemiology of Mucormycosis in the MENA region

Country	Clinical presentation	Study period	Setting	Incidence	Age of patients	Infected patients	Predisposing condition(s)	Agent	Diagnostic tool	Mortality rate	Ref
Lebanon	Rhino-orbito-cerebral disease; Disseminated disease	January 2008 and January 10, 2018	American University of Beirut Medical Center	0.83 cases/10,000 admissions	17–79 y	20	Hematological malignancies (acute myeloid, leukemia, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, and Hodgkin's lymphoma) Allogenic-HSCT DM	*Rhizopus* (44%) *Mucorales* spp. (44%) *Lichtheimia* spp. (12%)	Histopathology Culture	20%	[115]
Turkey	Rhino-cerebral infection (19.6%); Bone destruction (33.3%)	January 2003 to May 2013	Çukurova University Hospital	–	44.2 ± 18.2 y	51	Hematologic malignancies (52.9%) DM (25.5%) Solid malignancies (5.8%) Renal transplantation (1.9%) Pregnancy (1.9%)	–	–	52.9%	[139]
Turkey	Rhino-cerebral infection (60%); Disseminated infection (3.9%)	1995 and 2012	–	–	45.4 ± 21.4 y	151	Hematological malignancies (39.7%) Diabetes (49%)	*Mucor* spp. (37.2%) *Rhizopus* spp. (31.4%) Mucoromycetes (17.6%) *Rhizopus oryzae* (7.8%) *Rhizomucor* spp. (3.9%) *Rhizosporium* spp. (1.9%)	–	54.3%	[116]
Iran	Rhino-cerebral mucormycosis (95%)	2007 to 2017	Imam Reza Hospital in Tabriz	–	14–60 y	40	Diabetes (90%)	*Rhizopus* spp. (62.5%)	Clinical signs and symptoms, histopathology and culture	42.5%	[118]
Iran	Upper respiratory system (50%); Oral (40%); External otitis (10%)	2005 and 2010	Ali-Asghar Children Hospital	11.5%	7.95 y	10	Hematological malignancies (ALL (72.5%), AML (17.3%), Hodgkin lymphoma (5.8%), non-Hodgkin lymphoma (2.2%), Burkitt's lymphoma (1.1%))	Mucoromycetes (11.5%)	Local biopsy and pathology	53.3%	[120]
KSA	Sinus involvement (76.3%); Rhino-cerebral (3.4%); Disseminated (8.5%); Sino-pulmonary (11.9%)	2007–2017	Children's Cancer Hospital 57,357	–	8 y	45	Solid tumors (11%) AML (49%) ALL (37%) CML post-allogenic transplant (2%) Neutropenia (90%) Steroids (35%)	–	Histopathology (84%) Culture (4%) Both (12%)	33%	[124]

DM diabetes mellitus, *CML* chronic myeloid leukemia, *ALL* acute lymphocytic leukemia, *AML* acute myeloid leukemia, *KSA* Kingdom of Saudi Arabia, *allo-HSCT* allogeneic hematopoietic stem cell transplantation, *y* years the implementation of antimicrobial stewardship programs in this geographical area.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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