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REVIEW

# Clinical practice guidelines for the treatment of invasive *Aspergillus* infections in adults in the Middle East region: Expert panel recommendations

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## KEYWORDS

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**Summary** The incidence of invasive *Aspergillus* infections in the Middle East continues to rise with the increase in the number of immunocompromised patients, and carries significant morbidity and mortality. A panel of experts analysed the evidence from the most recent international guidelines and relevant published literature to reach consensus and develop clear clinical practice guidelines to aid diagnosis and treatment of invasive *Aspergillus* infections in the Middle East. Disease-specific recommendations were provided for the management of invasive aspergillosis. The

**Abbreviations:** ABCD, AMB colloidal dispersion; ABLC, AMB lipid complex; ABPA, allergic bronchopulmonary aspergillosis; AMB-D, amphotericin B deoxycholate; CNPA, chronic necrotising pulmonary aspergillosis; CNS, central nervous system; ECIL4, European Council on Infections in Leukaemia; GVHD, graft-versus-host disease; IA, invasive aspergillosis; IDSA, Infectious Disease Society of America; HEPA, high-efficiency particulate air filtration; L-AMB, liposomal amphotericin B; LFAB, lipid formulations of amphotericin B.

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expert panel acknowledged that these guidelines should be followed as closely as possible but used alongside clinical judgement.

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## Introduction

Invasive *Aspergillus* infections are a serious issue worldwide, including the Middle East region. They are associated with high morbidity and mortality and are a burden on healthcare services. Invasive aspergillosis (IA) is generally an opportunistic infection that affects immune-deficient patients and is related to defects in phagocytosis and T cells in number and/or function [1].

Invasive pulmonary aspergillosis and disseminated *Aspergillus* infections are the two most common forms of disease in severely immunocompromised individuals. Several other forms of aspergillosis have been described in immune

competent and/or less severely immunocompromised hosts. These include chronic necrotising pulmonary aspergillosis (CNPA), aspergilloma, allergic bronchopulmonary aspergillosis (ABPA) and *Aspergillus* sinusitis, which can be allergic, invasive or granulomatous. Single-organ involvement is well documented in the literature and includes eye, bone, joint, heart and skin and soft tissue aspergillosis [2].

Patients with acute leukaemia, solid organ transplant recipients and haematopoietic stem cell transplant recipients account for 29%, 9% and 32% of all *Aspergillus* infections, respectively [3]. Overall, nearly 30% of all invasive fungal infections in neutropenic patients undergoing cancer chemotherapy

are caused by *Aspergillus* spp [4]. Attributable mortality rates in patients with IA typically range from 30% to 60% [5–7]. The economic burden of aspergillosis-related hospitalisations is also considerable, even after the introduction of new antifungal treatments. In a study by Kim et al., costs and outcomes of IA-related hospitalisation relative to antifungal therapy were investigated [8]. The median length of stay was 23 days and the median hospital costs were \$52,803, with intravenous antifungals accounting for 7.2% (range: 0.78–15.9%) of the cost of aspergillosis-related hospitalisation.

Significant data have been published over the past two decades on various aspects of IA that include epidemiology, diagnosis and therapy in susceptible individuals. The field of antifungal agents for aspergillosis has expanded markedly in recent years amid the development of several classes of mould-active agents. These include several new-generation triazoles, echinocandins and less toxic formulations of amphotericin B.

Taking into account the lack of published regional studies, the limited diagnostic resources and other specific challenges facing the Middle East countries, an expert panel from the region reached consensus on treatment guidelines for invasive *Aspergillus* infections in the Middle East. These are the first treatment guidelines for invasive *Aspergillus* infections that have been produced for the region. Such regional guidelines for the treatment of IA are needed to account for the regional epidemiology of aspergillosis, available laboratory resources and treatment options.

## Methods

### Expert panel

A panel of experts met on June 15, 2012 in Dubai to reach consensus and develop clear clinical practice guidelines to aid diagnosis and treatment of invasive *Aspergillus* infections in the Middle East. The panel included specialists in infectious diseases and intensivists with expertise in the management of invasive *Aspergillus* infections.

### Evidence evaluation

Recommendations from the most recent international guidelines for invasive *Aspergillus* infections were reviewed prior to the expert panel meeting. The panel critically analysed recommendations from these guidelines and reviewed the available published literature on the diagnosis and treatment

**Table 1** Grading system.

| Grade | Definition  |
|-------|---|
| A     | Strongly recommended based on evidence from $\geq 1$ properly randomised, controlled trial  |
| B     | Recommended, based on evidence from $\geq 1$ well-designed clinical trial; from cohort or case-controlled analytic studies, from multiple case series |
| C     | Recommendation based on limited data from few retrospective case series, case reports, preclinical studies and expert opinion                         |

of invasive *Aspergillus* infections. These guidelines included the Infectious Disease Society of America (IDSA) guidelines on aspergillosis 2008 [9], the European Council on Infections in Leukaemia (ECIL4) 2011 update [10], and the Australian guidelines 2008 [11].

The validity, clinical relevance and applicability of the evidence for invasive *Aspergillus* infections in the Middle East were discussed. After considering the evidence, the panel achieved consensus on a number of recommendations that are supported by best scientific evidence.

## Levels of recommendation

The panel reviewed several grading systems for recommendations and agreed on a three-tier grading system: Grade A supports a strong recommendation based on evidence from at least one randomised controlled clinical trial to Grade C for which there are limited data to support a recommendation (Table 1).

## Guideline development

The discussions and consensus statements were recorded at the meeting and written up as a full manuscript draft by a professional medical writer. The panel reviewed, edited, and provided comments on the outline and manuscript drafts until a final version was reached, which was approved by all members.

## Epidemiology of invasive *Aspergillus* infections in the Middle East region

### Incidence

*Aspergillus* spp. are the most commonly isolated invasive moulds [12]. In the Middle East region, invasive *Aspergillus* infections are well documented and are probably on the rise [13,14], in part due to evolving medical practice with an increase in the number of immunocompromised patients due to cancer treatment, organ transplantation and chronic immunosuppressive therapy. However, it is difficult to accurately assess mortality related to invasive *Aspergillus* infections in the Middle East region due to the nature of the studies published (primarily case studies). The lack of epidemiological data for *Aspergillus* infections in the region is also related to the diagnostic limitations due to the limited capability of many laboratories to recover and identify these organisms from studied specimens.

### Mortality

Invasive *Aspergillus* infections are an important cause of morbidity and mortality of hospitalised patients. Mortality from invasive *Aspergillus* infections is variable and depends on the patient's underlying condition, site of infection and timing and selection of therapy. Mortality can be as high as 90% in stem cell recipients with disseminated and central nervous system (CNS) disease [15]. Data from prospective trials indicate that overall early mortality (12 weeks on antifungal therapy) of all disease entities ranges from 30% to 40% [16,17].

### Species distribution

Contrary to other parts of the world, *Aspergillus flavus*, not *Aspergillus fumigatus*, is the most commonly reported species causing invasive *Aspergillus* infections in the Middle East region [18–20]. *Aspergillus terreus* may be more common than *A. fumigatus*. In Asia, Africa and the Middle East, sinus aspergillosis and *Aspergillus* endophthalmitis are well described [18]. Alongside classical risk factors for invasive *Aspergillus*, e.g. prolonged neutropenia, organ transplantation, graft-versus-host disease (GVHD) and immunosuppression, other risk factors have been documented such as chronic obstructive pulmonary disease, liver failure and tuberculosis [18]. Similar to data reported elsewhere, pulmonary and disseminated disease are the two most commonly encountered forms of IA in

patients with haematological malignancies, recipients of allogeneic stem cell transplant and solid organ transplantation.

### Diagnosis of invasive *Aspergillus* infections

Rapid diagnosis of invasive *Aspergillus* infections, ideally to species level, is very important for favourable clinical outcome as other moulds and resistant *Aspergillus* spp. can lead to failure of antifungal therapy. Diagnosis of *Aspergillus* infections are based on a combination of clinical risks, symptoms and signs, culture, histopathology and detection of the fungal components such as the cell wall antigen galactomannan. The expert panel agreed that the most recent definitions of invasive fungal disease from the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [21] should be used as the reference standard in the Middle East region. However, for individual patient management, therapy can be initiated based on clinical judgement of the treating physician without fulfilling disease definition.

The criterion for proven invasive *Aspergillus* infection is the demonstration of fungal elements in disease tissue of most conditions. This could be through:

- A sterile specimen obtained by needle aspiration of biopsy for microscopic analysis that would demonstrate presence of hyphae accompanied by evidence of associated tissue damage.
- The recovery of a mould by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen and urine.

For an infection to be deemed probable, a host factor, clinical feature and mycological evidence would be required. A possible infection requires a host factor and a clinical feature without mycological evidence (Table 2). The criteria should be applied wherever possible, utilising expert advice and resources where appropriate.

The expert panel acknowledged that not all pathology laboratories in the Middle East region have access to the relevant equipment and diagnostic tests. Therefore, a local reference laboratory should be utilised if resources are not available in a local hospital. Serological tests, *Aspergillus*

**Table 2** Criteria for probable and possible invasive *Aspergillus* infections.

| Host factors  | Clinical criteria   | Mycological criteria <sup>a</sup>  |
|---|---|--|
| Recent history of neutropenia (<0.5 × 10 <sup>9</sup> neutrophils/L [ $<500$ neutrophils/mm <sup>3</sup> ] for >10 days) temporally related to the onset of fungal disease<br>Receipt of an allogeneic stem cell transplant | <i>Lower respiratory tract fungal disease</i><br>The presence of 1 of the following 3 signs on CT:<br><ul style="list-style-type: none"> <li>• Dense, well-circumscribed lesion(s) with or without a halo sign</li> <li>• Air crescent sign</li> <li>• Cavity</li> </ul>  | <i>Direct test</i><br>Mould in sputum, bronchoalveolar lavage fluid, bronchial brush or sinus aspirate samples, indicated by 1 of the following:<br><ul style="list-style-type: none"> <li>• Presence of fungal elements by cytology, direct microscopy or culture indicating a mould</li> <li>• Recovery of a mould by culture</li> </ul> |
| Prolonged use of corticosteroids (excluding among patients with ABPA) at a mean minimum dose of 0.3 mg/kg/day or prednisone equivalent for >3 weeks   | <i>Tracheobronchitis</i><br>Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis.  | <i>Indirect tests (standardised and validated)</i><br><ul style="list-style-type: none"> <li>• Detection of galactomannan antigen in plasma, serum, bronchoalveolar lavage fluid or cerebrospinal fluid (CSF)</li> <li>• <math>\beta</math>-D-glucan detected in serum</li> </ul>  |
| Treatment with other recognised T cell immunosuppressants, such as cyclosporine, TNF- $\alpha$ blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days              | <i>Sinonasal infection</i><br>Imaging showing sinusitis plus at least 1 of the following 3 signs:<br><ul style="list-style-type: none"> <li>• Acute localised pain (including pain radiating to the eye)</li> <li>• Nasal ulcer with black eschar</li> <li>• Extension from the paranasal sinus across bony barriers, including into the orbit</li> </ul> |  |
| Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)   | <i>CNS infection</i><br>1 of the following 2 signs:<br><ul style="list-style-type: none"> <li>• Focal lesions on imaging</li> <li>• Meningeal enhancement on MRI or CT</li> </ul>   |  |

Adapted from Ben de Pauw et al. [21] *Clin Infect Dis.* 2008;46(12):1813–21. ABPA, allergic bronchopulmonary aspergillosis; CNS, central nervous system.

<sup>a</sup> Required for probable, not possible, invasive *Aspergillus* infections.

galactomannan and  $\beta$ -D-glucan, and *Aspergillus* DNA detection by polymerase chain reaction (PCR) or microarray are useful tests in the early diagnosis of IA. The panel recommends that the serological tests of *Aspergillus* galactomannan and  $\beta$ -D-glucan be available in typical tertiary care centres with a high number of patients at risk for IA. National and regional collaboration for such diagnostic tests is highly recommended.

*Aspergillus* galactomannan has good sensitivity and very good specificity for the diagnosis of IA in patients with haematological cancer and haematopoietic stem cell transplant recipients. Sensitivity is in the range of 65–90% and specificity of about 95% with a cut-off level of 0.5 in serum [22]. Progressive increase in serum *Aspergillus* antigen levels over time signifies failure of treatment [23]. In addition, a few studies demonstrated that *Aspergillus* galactomannan from respiratory secretions obtained by bronchoalveolar lavage has

better sensitivity than *Aspergillus* galactomannan from serum in the diagnosis of invasive pulmonary aspergillosis [24]. The expert panel recommends that this diagnostic test be done whenever feasible. However, antifungal therapy should not necessarily be discontinued once galactomannan antigenaemia returns to a normal level [9].  $\beta$ -D-glucan is a cell wall antigen that is common to most fungi. Studies indicate good sensitivity of  $\beta$ -D-glucan for invasive fungal infections including aspergillosis. However, specificity is relatively low for aspergillosis and false positive tests have occurred in bacterial infections and patients on haemodialysis [25]. There are currently no data to suggest its use to monitor response to antifungal therapy. *Aspergillus* DNA detection by real-time PCR is promising in the early diagnosis of IA; however, it is not widely used in clinical practice. Imaging through high-resolution CT scan of the chest has been shown to aid in the early detection of early lung lesions that suggest

aspergillosis [26–29]. The expert panel recommends that it should be considered early in patients at risk of IA.

### Consensus recommendations for treatment of disease-specific *Aspergillus* infections

The following agents have been approved by the Food and Drug Administration (FDA) in the United States of America and the European Medicines Agency for the treatment of IA: Amphotericin B deoxycholate (AMB-D) and the lipid formulations (AMB lipid complex [ABLCL], liposomal amphotericin B [L-AMB] and AMB colloidal dispersion [ABCD]), itraconazole, voriconazole, posaconazole and caspofungin. Treatment of IA should be aggressive and started early upon suspecting the disease as delayed therapy is associated with worse outcome (A). Voriconazole is the first-line therapy in most conditions, followed by other licensed antifungal therapy as published data have shown better efficacy compared with AMB-D. A large prospective, randomised trial for the treatment of invasive pulmonary aspergillosis demonstrated that voriconazole was superior to AMB-D [30]. L-AMB was studied in lower and higher doses in a prospective randomised trial and showed equal efficacy of both doses in IA. Other agents such as the echinocandins, ABLCL and other triazoles were studied in non-randomised prospective salvage therapy trials. A different class of antifungals should be considered for therapy in patients on mould-active prophylactic antifungal treatment. In the Middle East region, treatment of IA is often determined by economic pressures. As a result, many public-sector hospitals may use AMB-D or itraconazole due to limited resources and limited access to more costly antifungals. Periodic testing for liver and renal functions is recommended to monitor for antifungal toxicity.

#### Invasive pulmonary aspergillosis

Voriconazole (A) is strongly recommended as primary therapy. The superiority of voriconazole over AMB-D was demonstrated in the largest prospective, randomised trial for the treatment of invasive pulmonary aspergillosis [30]. Its efficacy in paediatric and adult patients refractory to or intolerant of conventional antifungal therapy was further demonstrated in other trials [31–33]. Lipid formulations of amphotericin B (LFAB) (B), caspofungin (B), micafungin (B), posaconazole (B), itraconazole (B) and AMB-D can be used as an alternative

in case of failure, intolerance or unavailability of voriconazole. L-AMB, ABLCL, caspofungin or micafungin and AMB-D should be used initially in patients on voriconazole prophylaxis.

Evaluation of clinical signs and symptoms and periodic radiographic imaging are key elements of therapeutic monitoring of invasive pulmonary aspergillosis. Response to therapy can be monitored using serial serum *Aspergillus* galactomannan and CT scan of the chest.

Despite medical therapy with voriconazole, IA of the heart, great vessels, pleural space and bone usually warrants surgical intervention. Surgical resection of pulmonary lesions due to *Aspergillus* spp. can be useful for definitive diagnosis and potential localised eradication (B). In the case of solitary lung lesions, resection of the lesion or lobectomy may be warranted, especially in patients with haemoptysis [27,34,35]. Surgical therapy should also be considered for patients with chest wall invasion or with lesions located close to the pericardium or the great vessels. This can prevent erosion of pulmonary lesions into the great vessels and pericardial space as well as relieve pain and prevent pleurocutaneous fistula.

In patients undergoing chronic immunosuppressive therapies, the panel agreed that antifungal therapy should be continued throughout the duration of immunosuppression as this seems to be associated with a more favourable outcome (B). This should be guided by radiologic resolution of *Aspergillus* lesions. Withdrawing or reducing the dose of corticosteroids is advisable in IA (C). Recurrent infection can be prevented by resuming antifungal therapy in patients successfully treated for IA in the past who will require future immunosuppressive therapy, especially when leading to neutropenia (B) [36,37].

#### Tracheobronchial aspergillosis

Tracheobronchial involvement is an uncommon form of invasive pulmonary aspergillosis. Early treatment may prevent anastomotic disruption and loss of the lung graft. The panel recommended voriconazole (B) as primary therapy and LFAB (C) as alternative therapy. Little data are available on the use of echinocandins or posaconazole (C). Aerosolised LFAB may be considered to deliver high concentrations of polyene therapy to the infected site (C).

#### Invasive sinus aspergillosis

Voriconazole (C) can be used as a first-line treatment when the infection is known to be due to

*Aspergillus* [38]. Posaconazole and itraconazole (C) are a suitable alternative treatment. However, given that voriconazole and itraconazole lack clinical activity against sinonasal zygomycosis, LFAB or AMB-D (B) can be started when the diagnosis of aspergillosis cannot be confirmed and sinonasal zygomycosis cannot be ruled out. Surgical referral early on is critical in most cases of invasive fungal sinusitis (B). The resection of the infected tissues and/or the extent of debridement will vary and is based on the extent of disease and the patient's condition.

### Chronic necrotising pulmonary aspergillosis (CNPA)

Based on the limited number of studies for the treatment of CNPA [39–43], the expert panel recommends the use of orally administered itraconazole (C), posaconazole (C) or voriconazole (C) as a first-line treatment. L-AMB (C), ABLC (C), caspofungin (C) and micafungin (C) can be used as alternatives. The duration of therapy is variable and depends on the clinical and radiological response. In most instances therapy is required for 3–6 months, which warrants the use of oral antifungal therapy.

### Aspergillosis of the CNS

CNS aspergillosis is the most devastating infectious manifestation caused by *Aspergillus* spp. The evidence regarding effective systemic therapy for aspergillosis of the CNS supports the use of voriconazole (B) as the first-line treatment [44]. Alternative therapies for those refractory to voriconazole include posaconazole (C), LFAB (C) and itraconazole (C). Surgical resection may be needed for diagnosis and could aid in response to antifungal therapy [45,46]. Resection of the infected tissue and the extent of debridement may vary based on location, neurological sequelae, accessibility and surgical judgement.

### *Aspergillus* infections of the heart (endocarditis, pericarditis, myocarditis)

Cardiac aspergillosis carries a poor prognosis. Timely and aggressive treatment is paramount for a successful outcome. The expert panel recommended LFAB (B) and AMB-D (B) as first-line treatment. Voriconazole (C), caspofungin (C), micafungin (C), posaconazole (C) and itraconazole (C) can be used as alternatives.

Combined antifungal therapy and surgical resection of the infected valve or mural lesion can lead to successful management of *Aspergillus* endocarditis. Surgical debridement is imperative for the survival of almost all cases of *Aspergillus* endocarditis and most patients are treated with amphotericin [47–49]. Systemic antifungal therapy is the preferred treatment approach for *Aspergillus* myocarditis as it usually occurs in cases of disseminated disease. In pericarditis, pericardiectomy reduces organism burden around the heart and may prevent tamponade.

Antifungal therapy for aspergillosis of the heart should be continued for not less than 6 weeks after surgical intervention (C). Patients with a history of infected prosthetic valve are at risk for recurrent infections. In such case, lifelong antifungal therapy with an antifungal triazole, such as oral voriconazole or posaconazole (C), should be considered.

### *Aspergillus* osteomyelitis and septic arthritis

*Aspergillus* osteomyelitis and arthritis usually require a combination of systemic antifungal therapy and surgical management. First-line therapies are voriconazole (B), AMB-D (B) and surgery. L-AMB (B), ABLC (B), caspofungin (B), micafungin (B), posaconazole (B) and itraconazole (B) can be used as alternatives following failure of voriconazole. There is a role for surgical debridement of the infected bone and surgical evaluation determines the extent of surgery [50]. Successful treatment of *Aspergillus* arthritis often results from a combination of medical therapy and drainage of the joint based on the clinical presentation and requires 6 weeks or more of antifungal therapy [51].

### *Aspergillus* infections of the eye (endophthalmitis and keratitis)

*Aspergillus* endophthalmitis and keratitis are devastating infections that may result in vision loss for those affected. AMB-D (B) and voriconazole (B) can be used as first-line treatment. Alternatives include L-AMB (B), ABLC (B), posaconazole (C), itraconazole (C), caspofungin (C) and micafungin (C). Treatment of *Aspergillus* endophthalmitis with intravenous AMB or intravitreal AMB plus vitrectomy may be sight saving. Systemic or intravitreal injection of voriconazole should be considered as second-line therapy [52,53]. Ophthalmologic surgical intervention is warranted in cases with potential for corneal perforation or disease progression despite

medical therapy. Management of *Aspergillus* keratitis requires emergency ophthalmologic intervention with ophthalmologic examination, topical antifungal therapy, and systemic antifungal therapy with AMB, voriconazole or itraconazole [9]. Surgical intervention, including debridement, lamellar keratectomy or a conjunctival flap, is often required. If the cornea remains infected despite topical therapy and there is a risk of corneal perforation, surgical resection and corneal transplantation might be necessary.

### Cutaneous aspergillosis

Cutaneous aspergillosis often results from secondary haematogenous dissemination in immunocompromised patients [54,55]. Systemic voriconazole (A) is recommended as first-line therapy. L-AMB (B), posaconazole (B), itraconazole (B) and echinocanins (B) are acceptable alternatives. Surgical intervention may be considered, particularly in primary cutaneous infection.

### *Aspergillus* peritonitis

Patients on peritoneal dialysis are at risk of *Aspergillus* peritonitis [56]. Dialysis catheter removal and medical management with intravenous and intraperitoneal AMB-D was recommended by the panel as first-line therapy. Alternative treatments are itraconazole (C), voriconazole (C), posaconazole (C) and LFAB (C).

Disease-specific guidelines and dosing recommendations for invasive aspergillosis are listed in Tables 3 and 4.

### Empirical antifungal therapy

Neutropenic patients with persistent fever despite antibacterial therapy are at significant risk of developing an invasive fungal infection. The importance of early initiation of AMB-D in these patients for the treatment of IA was highlighted in previous reports [57,58]. However, in later trials, L-AMB, caspofungin and itraconazole were found to be as effective as, but less nephrotoxic than, AMB-D [59–61]. The expert panel agreed that first-line therapies of probable aspergillosis in patients who are neutropenic with prolonged fever include L-AMB (A), caspofungin (A), voriconazole (A) and itraconazole (A). AMB-D (A) is recommended as an alternative therapy.

### Prophylaxis

Prophylactic treatment against IA remains a challenge as appropriate patient selection is difficult. According to the IDSA 2008 guidelines, the patients most likely to benefit from prophylaxis therapy are those with prolonged neutropenia and severe GVHD, lung transplant recipients, patients receiving long-term high-dose corticosteroid therapy, some liver transplant recipients and those with certain inherited immunodeficiency disorders. The recommended first-line treatment in patients at high risk for IA (i.e. haematopoietic stem cell transplantation recipients and patients with acute myelogenous leukaemia or myelodysplastic syndrome) is posaconazole (A). Voriconazole can be an alternative therapy in recipients of allogeneic bone marrow transplantation (A). Micafungin can be used in the pre-engraftment phase following HSCT (A). For patients refractory or intolerant to first-line therapy, itraconazole (B) and echinocandins are possible alternatives (C). The use of high-efficiency particulate air filtration (HEPA) filters for rooms or wards of neutropenic patients is highly recommended [62,63].

### Combination therapy

The expert panel agreed that there are insufficient data to recommend combination therapy for the treatment of invasive *Aspergillus* infections. Current data are mostly from retrospective studies and inconclusive. A recent large prospective randomised trial on the combination of anidulafungin and voriconazole versus voriconazole alone for therapy of IA was presented in abstract form. The study indicates a trend towards a better response with the combination regimen but did not reach statistical significance. This study cannot be evaluated until full publication [64].

### Duration of treatment

Duration of antifungal therapy for invasive pulmonary aspergillosis is not well defined. After review of the evidence the expert panel agreed that no fixed duration of therapy can be recommended for invasive *Aspergillus* infections. The treatment duration will depend on the individual patient, the site of infection, the extent of the disease and the immunosuppression status. Antifungal therapy may be continued for several months (a minimum of

**Table 3** Disease-specific guidelines.

| Condition   | Primary therapy  | Alternative therapy  |
|---|--|--|
| Invasive pulmonary aspergillosis  | Voriconazole (A)   | LFAB (B)<br>Caspofungin (B)<br>Micafungin (B)<br>Posaconazole (B)<br>Itraconazole (B)<br>Anidulafungin (C) |
| Tracheobronchial aspergillosis  | Voriconazole (B)   | LFAB (C)   |
| Invasive sinus aspergillosis <sup>a</sup>   | Voriconazole (C)   | Posaconazole (C)<br>LFAB (C)   |
| CNPA (subacute invasive pulmonary aspergillosis)  | Voriconazole (C)<br>Posaconazole (C)<br>Itraconazole (C) | LFAB (C)<br>Itraconazole (C)<br>Echinocandins (C)  |
| Aspergillosis of the CNS  | Voriconazole (B)   | L-AMB (C)<br>Posaconazole (C)<br>ABLC (C)<br>Itraconazole (C)  |
| <i>Aspergillus</i> infections of the heart (endocarditis, pericarditis and myocarditis) | LFAB (C)<br>AMB-D (C)                                    | Voriconazole (C)<br>Posaconazole (C)<br>Itraconazole (C)<br>Echinocandins (C)                              |
| <i>Aspergillus</i> osteomyelitis and septic arthritis                                   | Voriconazole (B)<br>AMB-D (B)                            | Similar to invasive pulmonary aspergillosis  |
| <i>Aspergillus</i> infections of the eye (endophthalmitis and keratitis)                | AMB-D (C)<br>Voriconazole (C)                            | Similar to invasive pulmonary aspergillosis; limited data with echinocandins                               |
| Cutaneous aspergillosis   | Voriconazole (A)   | Posaconazole (B)<br>Itraconazole (B)<br>LFAB (B)<br>Echinocandins (B)                                      |
| <i>Aspergillus</i> peritonitis  | AMB-D (C)  | Itraconazole (C)<br>Voriconazole (C)<br>Posaconazole (C)<br>LFAB (C)                                       |

AMB-D, amphotericin B deoxycholate; CNPA, chronic necrotising pulmonary aspergillosis; CNS, central nervous system; L-AMB, liposomal amphotericin B; LFAB, lipid formulations of amphotericin B.

<sup>a</sup> If Zygomycosis is suspected LFAB is the preferred initial therapy.

**Table 4** Dosing recommendations for invasive aspergillosis.

| Agent               | Dose   |
|---------------------|--|
| Micafungin          | 100 mg daily   |
| Anidulafungin       | 200 mg, then 100 mg daily  |
| Caspofungin         | Loading dose (LD) 70 mg, then 50 mg daily  |
| Voriconazole        | 6 mg/kg every 12 h for 2 doses, then 4 mg/kg every 12 h  |
| Posaconazole        | 200 mg three times a day. Alternatively, patients who can tolerate food or a nutritional supplement may take 400 mg (10 ml) twice a day during or immediately following a meal or nutritional supplement |
| Itraconazole (oral) | 200 mg twice daily in case of invasive or disseminated disease. Avoid stomach acid suppressants with capsule formulation.  |
| LFAMB               | 3–5 mg/kg daily  |
| AMB-D               | 0.5–1.0 mg/kg daily  |

AMB-D, amphotericin B deoxycholate; LFAM, lipid formulations of amphotericin B.

The expert panel recommends using the doses within the prescribing information unless otherwise stated.

6–12 weeks) when used alongside regular monitoring (B).

## Limitations and future direction

These guidelines summarise the consensus agreement of an expert panel for the treatment of invasive *Aspergillus* infections in the Middle East and are based on a review and analysis of the most recent international guidelines and published literature. The development of these guidelines was needed to guide clinicians in providing the best treatment while considering regional limitations in the areas of epidemiology, diagnosis and therapeutic options. The limited epidemiological data available from the Middle East highlight the need for appropriate reporting and documenting of the diagnosis of invasive *Aspergillus* infections. The diagnosis of infection in the region relies primarily on conventional techniques, such as microscopy and culture. The availability of tests such as galactomannan,  $\beta$ -D-glucan test and DNA detection of invasive *Aspergillus* infections is limited to a few centres. The expert panel agreed that every effort should be made to diagnose infections to a species level and a local reference laboratory should be utilised if resources are not available in a local hospital.

Members of the working group acknowledged that these guidelines should be followed as closely as possible and used alongside clinical judgement. Expert advice should be sought from local reference centres when required to fully diagnose and optimally treat invasive *Aspergillus* infection. While these recommendations will actively change in response to emerging data from the region, the expert panel hopes that their implementation will improve mortality rates from IA in the Middle East.

## Competing interests

The authors who contributed to this article have disclosed the following industry relationships: Dr. Adel Alothman reports receiving honorarium for lectures from Pfizer, MSD and Alhikma Companies. Dr. Tariq Al Musawi reports receiving honorarium for lectures from Pfizer, GSK, Astra Zeneca and MSD. Dr. Jameela Al Salman has nothing to declare. Dr. Muna Almaslamani reports receiving consultancy fees from Pfizer. Dr. Hail M. Al-Abdely and Dr. Nadine Yared report receiving honorarium for lectures from Pfizer and MSD. Dr. Adeel A. Butt reports receiving honorarium for lectures from Sanofi Aventis

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## Author contributions

All authors contributed extensively to the work presented in this manuscript. Dr. Al-Abdely led the development of the manuscript. All authors participated in the review, contributed to the content and approved all sections of the manuscript.

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