INFORM II

Integrated Networking FOrum for Research in Mycology

The 2nd ISHAM-Gilead Forum on FUNGAL INFECTIONS IN THE MIDDLE EAST

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INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

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The 2nd ISHAM-Gilead Forum on Fungal Infections in the Middle East
5th & 6th May 2017, Sofitel Downtown Hotel, Dubai, United Arab Emirates

SUMMARY

INFORM II
Integrated **N**etworking **FO**rum for **R**esearch in **M**ycology
5th & 6th May 2017
Sofitel Downtown Hotel
Dubai, United Arab Emirates

The 2nd ISHAM-Gilead Forum on Fungal Infections in the Middle East was held on 5–6 May 2017, in Dubai, UAE. The meeting provided an opportunity for Middle East clinicians involved in treating fungal disease to discuss the latest developments in best practice for the management of fungal infections with international experts, and be informed of the latest advances in research presented at European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2017.

The meeting was opened with a welcome address from Hail el-Abdely, head of the General Directorate of Infection Prevention and Control in the Saudi Arabia Ministry of Health and Professor of Medicine at Al Faisal University, Riyadh, Saudi Arabia, and Malcolm Richardson, President of the International Society for Human and Animal Mycology (ISHAM), who gave an overview of the aims of INFORM II as an interactive symposium and highlighted the topics to be presented at the meeting.

RISK FACTORS FOR IFD

Risk factors for IFD in immunocompromised patients
Johan Maertens

"The incidence of fungal infections in recent years has increased for some types of haematological malignancy…and decreased for others"

Immunocompromised patients are at increased risk of invasive fungal disease (IFD), particularly from moulds. Strategies for preventing IFD range from giving primary antifungal prophylaxis to high-risk patients to more targeted treatment of patients with probable or proven fungal infection. Patients with an identified fungal infection are often those with a higher burden of infection and higher mortality. The incidence of fungal infections in recent years has increased for some types of haematological malignancy (e.g. acute lymphoblastic leukaemia and non-Hodgkin lymphoma) and decreased for others (e.g. acute myeloid leukaemia and allogeneic haematopoietic stem cell transplantation [HSCT] patients),[1,2] suggesting that the risk of fungal infection varies between patient subgroups. The variation in risk of invasive mould disease between countries and different groups of patients with haematological malignancies is demonstrated by studies such as the international, observational PIMDA study.[3] However, there is currently no recommendation from ECIL on which patients should be given antifungal prophylaxis, and which would benefit more from a diagnostic-driven approach to treatment. The benefit of primary prophylaxis for a wide range of patients is supported by many studies, whereas the more recent diagnostic-driven approach is mostly used in haematology and intensive care patients.

Risk stratification allows antifungal prophylaxis to be targeted to the patients who will benefit most. Immunocompromised patients at risk of IFD can be classed as low, intermediate, or high risk, depending on multiple factors including primary host factors, the overall state of immunosuppression, the patient's innate immune status, environmental factors, and other factors such as co-morbidities.[4] Low-risk patients should be given fluconazole prophylaxis or none at all, while intermediate-risk patients should be given fluconazole prophylaxis, with monitoring of biomarkers to assess treatment efficacy, and high-risk patients should be given mould-active prophylaxis. Recent updates of ECIL guidelines (ECIL 5, 2013) give recommendations for antifungal use individualised to different patient groups,[5] enabling this risk stratification strategy to be used widely in clinical practice.

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DEBATE

Everyone in haematology deserves antifungal prophylaxis
Samir Agrawal (speaking for the motion)

"The key question is whether prevention of fungal infection is better than trying to cure it once established or whether treatment is better than prophylaxis?"

Is prevention of fungal infection better than trying to cure it once established or is treatment better than prophylaxis? Data from many randomised controlled trials and real-world studies show that antifungal prophylaxis reduces mortality, decreases the incidence of IFD,[6–11] reduces the duration of febrile days and hospital stay,[12–14] and decreases overall health costs.[15–17] Whether the available treatment options work as well in treating established IFD is more debatable. Furthermore, waiting to identify (suspected) fungal infection and then treat the patient, assumes that we can make a swift, accurate diagnosis—this is not the reality.

Mortality rates from established IFD remain very high, as shown in multiple studies,[2,18–20] and a large proportion of IFD confirmed from post-mortem autopsies were not diagnosed while the patient was alive.[21] Concerns over antifungal resistance need not be a barrier to prophylaxis in haematology, as it remains a rarity in clinical practice.

IFD is serious and can be difficult to treat, and the time taken to make a diagnosis of the infection can increase the risk of mortality. Prophylaxis is safe, well-tolerated and effective, and can be given to all haematology patients.

DEBATE

Peter Donnelly (speaking against the motion)

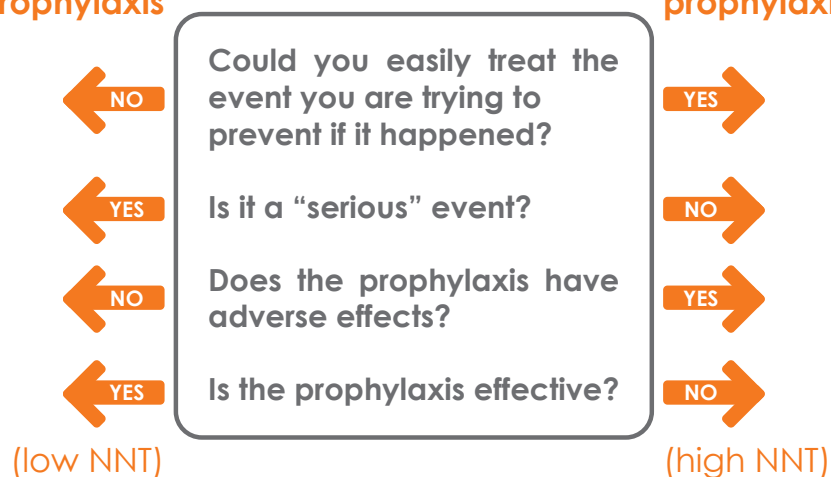**"…should you use a drug for prophylaxis just because you can use it?"**

Not everyone in haematology deserves prophylaxis because there are other approaches to managing the risk. The primary question is: should you use a drug for prophylaxis just because you can use it?

Bias toward prophylaxis

Bias against prophylaxis

NO ← **Could you easily treat the event you are trying to prevent if it happened?** → YES

YES ← **Is it a "serious" event?** → NO

NO ← **Does the prophylaxis have adverse effects?** → YES

YES ← **Is the prophylaxis effective?** → NO

(low NNT)

(high NNT)

McQuay & Moore, 1997 Ann Intern Med 126:712-720.

This all depends on whether the event you are trying to prevent can be treated easily if it occurs.[22] Invasive aspergillosis can indeed be managed effectively if detected sufficiently early, which can be achieved using empirical therapy for persistent fever and, increasingly, a diagnostic-driven approach based on detection of pulmonary abnormalities consistent with fungal disease, detection of galactomannan or nucleic acid by PCR, or both.[23] The second important aspect depends on the numbers needed to treat (NNT), which in turn is based on the estimated risk of infection. Risks for invasive fungal disease are typically less than 10% among haematology patients. So, to cut the risk by half would yield an NNT of 20. However, if the risk is closer to 5%, cutting this by half yields an NNT of 50. This may well be unacceptable if the number needed to harm (NNH) is lower, as is the case with posaconazole with a reported NNH of 20.[8] Moreover, as with empirical therapy, more patients would be given antifungal drugs than actually need them, putting pressure on budgets as well as increasing the risks of resistance and toxicity. Clearly prophylaxis forms an important part of antifungal management, but the decision on whether or not to employ it depends on a proper understanding of the risks, costs, and benefits, which requires centres to have a good idea of the infections their patients face at any given time.

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PANEL DISCUSSION

Q1. In the Middle East, the local incidence and epidemiology of fungal infections are not well known, diagnostics are not available in many medical centres caring for critically ill patients, and many countries do not have a good infrastructure. The challenge for us is how do countries where data are not available adopt these recommendations for risk assessment?

"…it will be a very expensive strategy if you are giving prophylaxis to every high-risk patient…"

Dr Johan Maertens and Dr Agrawal responded that lack of ready access to diagnostics was also an issuein their own countries of Belgium and the UK. Those who do not have access to diagnostic testing must use the alternative of empirical treatment.

The main challenge is what to do after giving prophylaxis-it will be a very expensive strategy if you are giving prophylaxis to every high-risk patient and many of them end up being treated also as a result of your empirical or even diagnostic-driven approach. This needs to be considered before launching into mould-active prophylaxis.

"We as a community ought to ask for proper funding to get the information to remove the uncertainty and fear that drives us to prescribe drugs the patient may not need…If you know that roughly one in five patients is going to develop an invasive fungal disease, you should have the necessary facilities for dealing with that at your disposal"—Peter Donnelly

Q2. What is the main difference in invasive fungal disease treatment and prophylaxis between adults and children? Could the panel compare and contrast?

Dr Samir Agrawal noted that although none of the panel treated children, all were aware that in paediatrics there are very few data supporting licensed products in children and only one antifungal is licensed for prophylaxis in children. Dosing of the various antifungal drugs is not the same in children as it is in adults, and diagnostics are also different in children. The appearance of chest CT scans, in particular, is not the same in children as in adults.

Dr Johan Maertens added that the other difference between adults and children is in the risk assessment of these patients. Studies have shown that younger patients are at lower risk than older patients, and their underlying diseases may be different as well. In transplantation, children are at lower risk than adult patients, which makes it difficult to look for forms of diagnostics tests—if their incidence of fungal disease is low, then their false-positivity rate will be much higher.

CANDIDURIA

Candiduria
Jack Sobel

"Diagnosis of candiduria has issues both in localising the source and anatomical site of the infection and in the lack of a reliable method of diagnosis."

Candiduria is rare (<1%) in normal patients, but is the most common urinary tract infection (UTI) in the intensive care unit setting and constitutes 10–15% of all nosocomial UTIs. The majority of infections involve C. albicans (~50%), with C. glabrata making up 25–35% and the remaining 8–30% consisting of C. tropicalis, C. parapsilosis, C. krusei, and C. guilliermondii. Predisposing factors for candiduria include diabetes, disturbances in urine flow, genitourinary tract instrumentation (where biofilm formation can occur), and Gram-negative bacterial UTI. Diagnosis of candiduria has issues both in localising the source and anatomical site of the infection and in the lack of a reliable method of diagnosis. Candiduria is due either to haematogenous renal candidiasis or, rarely, an ascending infection (from the bladder, pelvis, or renal parenchyma). In most febrile patients with candiduria and an indwelling catheter, the fever is not due to Candida infection.

Therapy for candiduria depends on the presentation. Asymptomatic candiduria does not require therapy unless an ascending infection of the kidney and candidaemia develops, or there is a possibility that it is a manifestation of disseminated candidiasis. Treatment of symptomatic candiduria depends on the Candida species causing the infection, the presumed site or source of infection, the likelihood of disseminated disease, and the presence of an obstruction or fungal ball. In all cases, the bladder catheter (if present) should be removed. The choice of antifungal should be guided both by the susceptibility and sensitivity of the fungus in vitro, and whether the drug reaches levels in urine above the minimal inhibitory concentration (MIC). Oral fluconazole reaches high concentrations in urine, whereas amphotericin B can be used as a bladder irrigation instead of oral dosing. Echinocandins have limited value in treating candiduria but remain an option, as some cases have shown successful treatment.[24] Urosepsis is treated by relieving any obstruction and giving per-nephrostomy irrigation with an antifungal (e.g. echinocandins or polyenes). Candiduria associated with fungus balls requires surgical intervention and irrigation through the nephrostomy tube with amphotericin B.

The case of a 63-year old female patient with complicated genitourinary candiduria illustrates the principles of treatment. She had severe inflammation of the bladder mucosa with extensive desquamation and erythema of the mucosa. She did not tolerate itraconazole and the C. krusei infection had an MIC of 2 mg/mL for voriconazole, so she was given daily bladder irrigation with amphotericin B solution (50 mg/mL) with simultaneous topical clotrimazole vaginal cream. The outcome was successful over the long term.

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FUSARIUM INFECTIONS

Fusarium infections in haematology
Arnaldo Colombo

"Clinical features are non-specific and distinction from aspergillosis and mucormycosis in patients with haematological malignancies may be difficult."

The genus Fusarium contains many species and is widely distributed in nature. Of note, it has been documented in soil, dust storms, and plants from several Middle Eastern countries.[25,26] Human fusariosis manifests as superficial, localised subcutaneous infections and, in severely immunosuppressed patients, sinus, lung, or disseminated disease.[27] Invasive fusariosis (IF) occurs predominantly in immunocompromised patients with haematological malignancies and HSCT under prolonged and severe neutropenia (>10 days with <500 neutrophils/mm^3) and/or corticosteroid therapy.[27,28]

Invasive fusariosis should be suspected in neutropenic patients with skin lesions, which are present in >60% of cases. Lesions are usually multiple, involve any body site, and vary from erythematous papular or nodular painful lesions to necrotic lesions similar to ecthyma gangrenosum. Fungaemia is present in ~50% of immunocompromised patients with IF. Pulmonary disease is usually documented in 50–70% of patients.[29–31] Clinical features are non-specific and distinction from aspergillosis and mucormycosis in patients with haematological malignancies may be difficult. Sinus involvement occurs in up to 30% of cases.[29–31] Eventually, it may affect the central nervous system, eye, bone, kidney, muscles, spleen, and liver.

Diagnosis relies on isolation of Fusarium from blood cultures or demonstration of fungal elements in tissue that is culture positive for Fusarium (especially skin lesions). Fungal biomarkers, such as galactomannan and β-d-glucan, are not specific and may be detected in serum samples of most patients with IF. [27,–32–34]

Liposomal amphotericin B and voriconazole are recommended, despite the limited in *vitro* susceptibility of a large number of *Fusarium* species to them.[35] Despite limited scientific evidence to support combination therapy, voriconazole and a lipid amphotericin B have been used as salvage therapy for treating refractory cases, especially if the patient remains neutropenic and there is progression of IF.[36]

Interactive case study
Khaled Alobaid

This case study described a rare presentation of renal fungus ball in an adult patient. Management of this fungal infection was challenging. The patient presented initially with obstructive uropathy and acute renal impairment due to retroperitoneal fibrosis, an autoimmune disease.

The presence of percutaneous nephrostomy to relieve the obstruction predisposed the patient to have fungus ball due to *Candida albicans*. The infection was treated with systemic fluconazole, amphotericin B irrigation through nephrostomy, and stent exchange. However, the infection relapsed. The persistent and refractory nature of infection despite proper therapy is due to several reasons.

Firstly, the patient was immunosuppressed due to treatment with steroids and rituximab. Secondly, biofilm formation in ureteric stent, nephrostomy tube, and inside the obstructed part of ureteric lumen reduced antifungal efficacy. This biofilm is a protective mechanism by *C. albicans* against the effect of antifungals. Lastly, the local irrigation by amphotericin B, as compared to surgical removal of fungus ball, was probably insufficient in eradicating the infection. The patient ultimately recovered by tapering steroids, postponing rituximab, exchanging his ureteric stent and nephrostomy tube, and treating with long-term systemic fluconazole.

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MYCOSES-RISKS

Common imported mycoses-risks for the Middle East
Thuy Le

"Endemic mycoses are difficult to diagnose because of diverse clinical features (with acute, chronic, and disseminated manifestations depending on the immune status of the host), low diagnostic yield, and are slow-growing in nature…the mortality on treatment is up to 30% with the disseminated form."

Endemic mycoses are infections caused by a group of fungi that share common characteristics of having a restricted geographical distribution, occupying specific ecological niches, are thermally dimorphic, and are capable of causing disease in both immunocompromised and healthy hosts. Infections with endemic mycoses are difficult to diagnose because of diverse clinical features (with acute, chronic, and disseminated manifestations depending on the immune status of the host), low diagnostic yield, and are slow-growing in nature.

These infections result in significant morbidities, and the mortality on treatment is up to 30% with the disseminated form. The increase in international travel, migration, immune suppressive therapy, and the wide spread of the HIV epidemic has resulted in an increase in the number of travel-related cases and outbreaks[37] and the overall incidence in endemic regions.[38–40]

The most common endemic mycoses include: histoplasmosis (caused predominantly by *Histoplasma capsulatum*) endemic in eastern United States, Central and South America; coccidioidomycosis (caused by *Coccidiodes immitis*) endemic in south-western United States (California, Arizona, New Mexico, and Texas), Brazil, Uruguay, and Argentina; blastomycosis (caused by *Blastomyces dermatiditis*) endemic in eastern United states along the Mississippi and Ohio River basins; and talaromycosis (caused by *Talaromyces marneffei*) endemic in all Southeast Asia, southern China, and north-eastern India.

Latent infections can last for years; therefore, short-term and long-term travel history and risk activities are an important part of clinical assessment. Increased knowledge of disease and geographic distribution can increase awareness of risks and measures to mitigate risks. Clinical suspicion enables early diagnosis and treatment and improves patient outcomes.

CASE STUDY

Interactive case study
Abdullah Al Hatmi

A 37-year-old male living in Oman was seen by his physician with complaints of cough, weight loss, skin lesions, body aches with bilateral lower limb weakness, and intermittent fever. The patient had travelled to Malaysia on several occasions. He was diagnosed with HIV infection, and cultures from blood and bone marrow grew fungus.

Diagnosis was based on culture and PCR-sequencing, which revealed *Talaromyces marneffei*. Treatment with liposomal amphotericin B resulted in complete cure. This case is reported for its rarity and unusual presentation to alert clinicians and microbiologists to consider *T. marneffei* as an aetiology in high-risk individuals.

The importance of this case is in raising awareness of imported talaromyces infection and treatment, since we have many people working in the Gulf region originating from different Asian countries. Our case is the first recorded diagnosis of *T. marneffei* in Oman.

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ECCMID 2017

Highlights from ECCMID, Vienna 2017
Cornelia Lass-Flörl

"Monitoring the evolution of azole-resistant *A. fumigatus* in Belgium (2015–2016) showed 4.1% of *A. fumigatus* were azole-resistant…"

"The first case of echinocandin resistance due to a point mutation in the *FKS1* gene in an *A. fumigatus* clinical isolate in a patient with chronic pulmonary aspergillosis has been described."

A *Candida auris* outbreak in a tertiary care hospital in England showed that adequate infection control measurements are of most importance to inhibit fungal spread [41] and that *C. auris* is able to produce biofilms [42]. Novel data from the Netherlands showed invasive pulmonary aspergillosis complicating influenza in critically ill patients being on rise [43]. The reasons are unclear yet. The drug SCY-078, a novel glucan synthesis inhibitor displayed activity against *C. auris*; however, the combination of SCY-078 with other antifungals showed no improved activity against azole resistant *Aspergillus fumigatus* in vitro [44].

The consensus criteria for diagnosis of allergic bronchopulmonary aspergillosis (ABPA) published by the ISHAM working group on ABPA in 2013 were evaluated and showed usefulness for the clinical routine, as 79% of patients (n=151) met the criteria [45]. In addition, new cut-off values for Aspergillus-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis were released [46].

The new commercial PCR kit (MycoGENIE®, Adem Tech) targeting *A. fumigatus* and the TR34/L98H mutation directly from pulmonary samples were evaluated and showed good performance for invasive aspergillosis diagnosis, with a higher sensitivity than culture [47]. A retrospective observational cohort study comparing the management and outcome of culture-positive invasive aspergillosis due to *Aspergillus fumigatus* with wildtype and non-wildtype triazole susceptibility showed the all-cause mortality within the resistant cohort being 85.7% compared with 36.2% in the azole-susceptible cohort (*p*=0.0174) [48].

Monitoring the evolution of azole-resistant *A. fumigatus* in Belgium (2015–2016) showed 4.1% of *A. fumigatus* were azole-resistant, the main resistance mechanism proved to be TR34/L98H (75%) and overall, no increase in the prevalence of azole resistance was seen [49]. Although improvements have been made in recent years regarding the molecular-based diagnosis of invasive aspergillosis, the issue of false positivity in applying fungal PCR has yet to be resolved [50]. The first case of echinocandin resistance due to a point mutation in the *FKS1* gene in an *A. fumigatus* clinical isolate in a patient with chronic pulmonary aspergillosis has been described [51].

ECCMID 2017

Highlights from ECCMID, Vienna 2017
Ana Alastruey-Izquierdo

"The emergence of antifungal resistance was discussed: on one hand, the emergence of echinocandin resistance in *Candida* (mainly *C. glabrata*), and on the other hand, the emergence of azole resistance in *A. fumigatus*."

Updates from EUCAST antifungal susceptibility testing with new versions of the definitive documents released in January 2017 and new breakpoints for *Candida* and itraconazole and Aspergillus and isavuconazole were presented. The emergence of antifungal resistance was discussed: on one hand, the emergence of echinocandin resistance in *Candida* (mainly *C. glabrata*), which has nearly tripled between 2008 and 2015, and on the other hand, the advances in surveillance of azole resistance in *A. fumigatus*.[52,53]

A commercial agar-based method to screen for azole resistance in *A. fumigatus* was presented[54] and compared with e-test and EUCAST with good correlation. The effect of different types of plates and storage time for susceptibility testing was also evaluated.[55]

A new antifungal compound F901318 demonstrated good activity against resistant species of *Scedosporium* and *Lomentospora* as well as cryptic species of *Aspergillus*.[56,57]

An outbreak by antifungal-resistant *Candida auris* taking place in a Spanish hospital was also presented with close to 50 candidaemia cases.[58] A qPCR to detect clinically relevant Aspergillus was evaluated in bronchoalveolar lavage samples with 94.1% sensitivity and 76.5% specificity.[59]

A new strategy to differentiate colonisation from infection in Pneumocystis jirovecii using the rate of expression of two different genes showed promising results to tackle this important clinical problem.[60]

Patients suffering from COPD affected with *Aspergillus* compared with those not infected were differentiated with the electronic nose technology with a sensitivity of 91% and specificity of 90%.[61]

Finally, interesting results were presented evaluating a genetic variant probably related to ABPA, showing that patients with a mutation in this gene are related with higher fungal loads.[62]

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INVASIVE ASPERGILLOSIS

Invasive aspergillosis and influenza in the ICU: a case study
Paul Verweij

"The global epidemiology of invasive fungal infections in the ICU appears to be changing with invasive fungal diseases being diagnosed in patients with heterogeneous underlying diseases."

"A recent Dutch survey showed IAA in 16% of influenza patients in the ICU, many of which had no underlying disease or a disease with low risk for invasive fungal infection."

"Diagnostic delay may contribute to the mortality rate of 50–60%. In ICU patients with influenza, early bronchoscopy and fungal diagnostic are important in patients with suspected secondary infection."

The global epidemiology of invasive fungal infections in the ICU appears to be changing with invasive fungal diseases being diagnosed in patients with heterogeneous underlying diseases. In addition to well-known patient risk groups such as those with haematological malignancy and solid organ transplant recipients, other patients are developing invasive fungal disease, such as those receiving biologicals, patients with chronic lung disease (COPD), and in association with severe influenza pneumonia. Similar patterns in epidemiology are observed in the Middle East,[63,64] and fungal infection has become a significant burden in the ICU. Early initiation of appropriate antifungal therapy is critical to reduce mortality,[65] but early diagnosis is often difficult in the ICU-setting. The available diagnostic tools and current treatment recommendations were reviewed with an important role for biomarker-based, diagnostic-driven treatment approaches, as these may enable the most effective use of available therapies.[66]

A case study was presented of a patient with influenza associated invasive aspergillosis (IAA). A recent Dutch survey showed IAA in 16% of influenza patients in the ICU, many of which had no underlying disease or a disease with low risk for invasive fungal infection. The clinical presentation may be atypical due to the fact that unlike in neutropenia, these patients develop *Aspergillus* tracheobronchitis, which gives uncharacteristic CT lesions. Diagnostic delay may contribute to the mortality rate of 50–60%.[67] In ICU patients with influenza, early bronchoscopy and fungal diagnostic are important in patients with suspected secondary infection.

PANEL DISCUSSION

Q1. Regarding Dr Paul Verweij's recommendation of first-line treatment in his country (the Netherlands) of voriconazole plus echinocandin, if echinocandin was added in case of azole resistance being present, why is voriconazole also being used and not just echinocandin alone?

Dr Paul Verweij responded that they don't trust the use of either of these two drugs alone because studies in neutropenic patients show that voriconazole is not a good treatment to give as monotherapy. In non-neutropenic patients it might be better, but there are no data to confirm that, so combination therapy is given.

One study looked at combination therapy of voriconazole and anidulafungin against invasive aspergillosis and though the outcome wasn't conclusive, there was a trend suggesting that it was a good combination to give. Animal models have found that the combination works in azole-resistant isolates. The only concern is that some of these isolates are fully resistant to voriconazole, so that is why liposomal amphotericin B alone or in combination with voriconazole is also considered. For example, patients with mixed infection will have multiple lesions, and each lesion originates from a spore, which might be genetically different. So patients who we thought had a susceptible infection and were treated with voriconazole responded to treatment, because several susceptible lesions responded, but the resistant lesions did not. Some of these patients had dissemination to the brain, which then has resistant isolates, therefore we have to be really careful in these situations because it is difficult to exclude resistance in these patients.

Q2: In this region (Middle East), therapeutic drug monitoring (TDM) is not available, so what practical advice would you give us, in the regional country, if we do not have access to do TDM for voriconazole?

"…there are a lot of possibilities for interaction, so if access to TDM was not available, it might be better to choose another drug…"

Dr Paul Verweij responded that was a difficult question because there are a lot of possibilities for interaction, so if access to TDM was not available, it might be better to choose another drug, such as liposomal amphotericin B. He found that there is a very strong interaction between voriconazole and flucloxacillin, so if these drugs are given together, half the patients will not have measurable voriconazole levels. If you can't measure the drug exposure, then you need to be very careful with these patients as they need to be treated properly from the beginning.

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PANEL DISCUSSION

Q3: The risk of mortality increases by 1.64 for every hour of delay in giving the antifungal treatment. If you need to make clinical decisions in a short time frame, 1) why should I use combination therapy, especially if I'm using voriconazole, and 2) if I am seeing multinational patients with different colonisations of *Candida* infection and in my hospital azole resistance is not seen very often, should I use azoles from the beginning of treatment?

"…in intensive care, you don't have the time, so initial treatment with liposomal amphotericin B would also be a very good option and is recommended in intensive care units."

Dr Paul Verweij responded that following the clinical guidelines, voriconazole is the first choice of treatment; however, this is now being reconsidered given the resistance problems emerging, so risks and benefits must be weighed up.
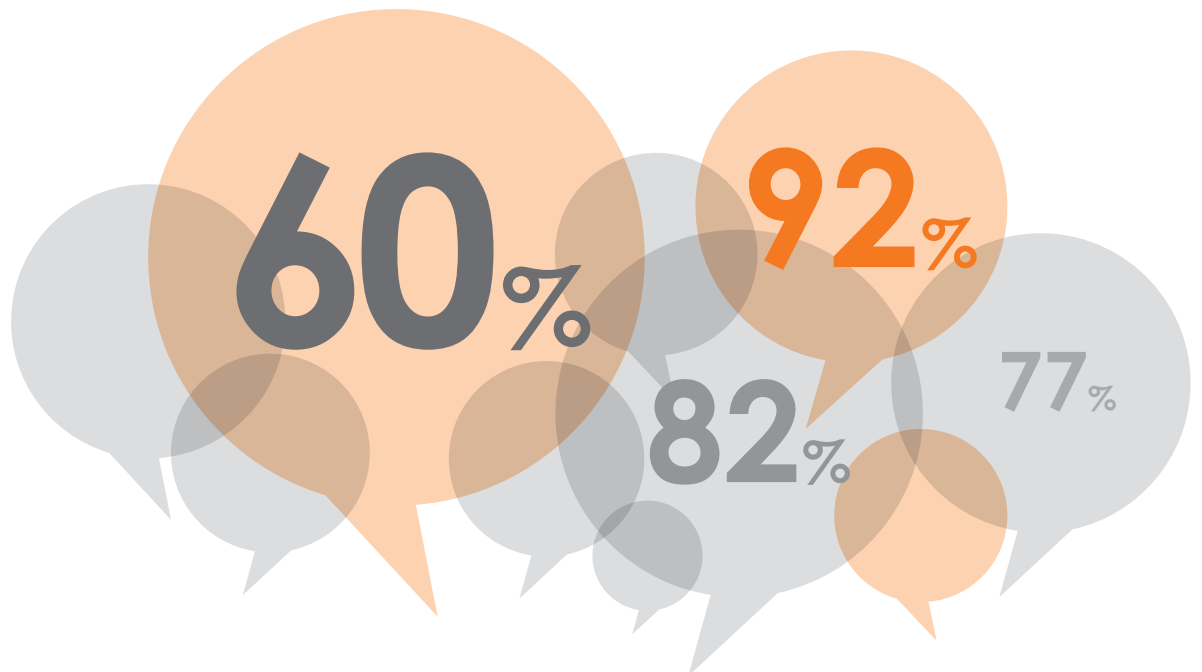

For example in paediatrics, you start treatment with voriconazole and AmBisome together, and in haematology voriconazole is still used because these patients are very intensely monitored, so if resistance is seen, the strategies can be changed quickly. However in intensive care, you don't have the time, so initial treatment with liposomal amphotericin B would also be a very good option and is recommended in intensive care units. You have to do what works for the situation, and take factors such as resistance and access to TDM into account. If you have a very heterogeneous group coming in from areas where you don't know the local epidemiology then it is wise to adapt your strategy to that situation.

THOUGHT

What the attendees thought

The attendees were pleased with the meeting overall, with more than 60% rating the agenda as 'excellent'. The majority of attendees (92%) rated the interactive activities as 'good' or 'excellent', and 92% were happy with the time they had for discussion. Most of the delegates (82%) agreed that the relevance of the programme to their clinical practice was 'good' or 'excellent'. The majority (77%) of attendees were keen to participate in future INFORM meetings.

60%   **92%**

82%   **77%**

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REMARKS

Concluding remarks

"Candiduria is extremely common and associated with considerable morbidity. Treatment of symptomatic candiduria, in spite of an increase in antifungals, is problematic!"

"The risk–benefit balance for antifungal prophylaxis is not the same for all immunocompromised patients. Risk stratification allows prophylaxis to be targeted to patients who will benefit most"—Paul Maertens

"Invasive fungal disease is serious and can be difficult to treat. Antifungal prophylaxis is safe, well-tolerated, and effective. Therefore everyone in haematology deserves antifungal prophylaxis"—Samir Agrawal

"Everyone in haematology does not deserve antifungal prophylaxis, BUT they all deserve proper measures to prevent invasive fungal disease!"—Peter Donnelly

"Candiduria is extremely common and associated with considerable morbidity. Treatment of symptomatic candiduria, in spite of an increase in antifungals, is problematic!"—Jack Sobel

"Invasive fusariosis should be included in the differential diagnosis of all haematological patients with multiple skin lesions and respiratory tract infections after prolonged exposure to neutropenia and/or high-dose steroids. Clinical management should include control of immunosuppression and early therapy with liposomal amphotericin B or voriconazole"—Arnaldo Colombo

"A multidisciplinary approach is essential in managing invasive fungal infections, especially in immunocompromised patients, as is knowing the pharmacokinetics of each fungal agent and using them accordingly. One size does not fit all!"—Khaled Alobaid
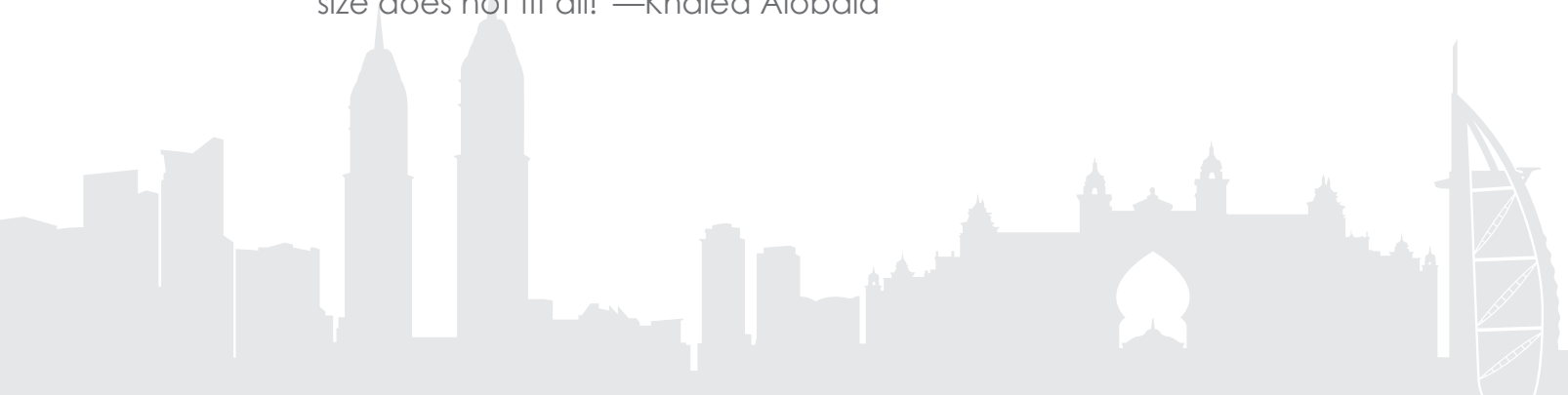
REMARKS

"Endemic mycoses are emerging infections in travellers—in particular, in people with compromised cellular immunity. Clinical suspicion enables early diagnosis and treatment and improves patient outcome"—Thuy Le

"Infection by *Talaromyces marneffei* is fatal if left untreated. The successful treatment of patients requires prolonged therapy. The continuing epidemic of HIV infection suggests that there will be a concomitant increase in the frequency of disease—be alert for imported cases of talaromycosis in the Middle East"—Abdullah Al Hatmi

"Trends from the 2017 ECCMID meeting included new antifungals, new diagnostics, and new markers for personalised medicine. Outbreaks of *Candida auris* are a new cause for concern, as are reports of resistance to echinocandins in *Candida glabrata* and to azoles in *Aspergillus fumigatus*"—Cornelia Lass-Flörl and Ana Alastruey-Izquierdo

"Prompt diagnosis and early, effective treatment is essential for patients in the ICU. Biomarker-based diagnostic-driven treatment approaches are replacing prophylactic and empirical treatment, and enable the most effective use of the available therapies"—Paul Verweij

The 2nd ISHAM-Gilead Forum on Fungal
Infections in the Middle East
5th & 6th May 2017, Sofitel Downtown Hotel, Dubai, United Arab Emirates

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