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Review Article

2016 guideline strategies for the use of antifungal agents in patients with hematological malignancies or hematopoietic stem cell transplantation recipients in Taiwan

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Abstract The Infectious Diseases Society of Taiwan (IDST), the Hematology Society of Taiwan, the Taiwan Society of Blood and Marrow Transplantation, Medical Foundation in Memory of Dr. Deh-Lin Cheng, Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education, and CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines cooperatively published this guideline for the use of antifungal agents in hematological patients with invasive fungal diseases (IFDs) in Taiwan. The guideline is the first one endorsed by IDST focusing on selection of antifungal strategies, including prophylaxis, empirical (or symptom-driven) and pre-emptive (or diagnostic-driven) strategy. We suggest a risk-adapted dynamic strategy and provide an algorithm to facilitate decision making in population level as well as for individual patient. Risk assessment and management accordingly is explicitly emphasized. In addition, we highlight the importance of diagnosis in each antifungal strategy among five elements of the antimicrobial stewardship (diagnosis, drug, dose, de-escalation and duration). The rationale, purpose, and key recommendations for the choice of antifungal strategy are summarized, with concise review of international guidelines or recommendation, key original articles and local epidemiology reports. We point out the interaction and influence between elements of recommendations and limitation of and gap between evidences and daily practice. The guideline balances the quality of evidence and feasibility of recommendation in clinical practice. Finally, this version introduces the concept of health economics and provides data translated from local disease burdens. All these contents hopefully facilitate transparency and accountability in medical decision-making, improvements in clinical care and health outcomes, and appropriateness of medical resource allocation.

Introduction

Invasive fungal diseases (IFDs) are increasing as a result of advances in health care and are associated with significant morbidity and mortality in susceptible patient populations.[1–6] The clinical constraints that preclude or delay timely interventions for underlying diseases, and suboptimal diagnostic tools available for diagnosis of IFDs have driven the overuse of empirical and prophylactic antifungal agents during the past two decades. The adverse effects of antifungal including direct toxicities, drug—drug interactions, emergence of antifungal resistance, and high costs complicate matters. These are the principal justifications for the need to develop better strategies for optimal use of antifungal agents.[7]

This guideline provides recommendation for antifungal strategies, including prophylactic, empirical (symptom-driven) and pre-emptive (diagnostic-driven), to prevent IFDs or reduce IFDs-related mortality or resource utilization in adult patients with hematological malignancies and hematopoietic stem cell transplant (HSCT) recipients who are at risk of developing IFDs (target population). The guideline is intended for all clinicians who are likely to provide health care for target populations and to identify quality improvement opportunities. This guideline takes into consideration the heterogeneity of pathogens, patient population and clinical scenarios in order to facilitate decision making for individual patients and to create explicit and feasible recommendations to implement in clinical practice. The goals are to promote judicious and optimal use of antifungal agents, facilitate the rationale of selecting antifungal strategy, and emphasize risk assessment and management.

Clinical practice guidelines are considered to be the essence of evidence-based medicine. They were defined by the Institute of Medicine, USA, in 1990 as "systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances."[8] The first and second version of the antifungal guidelines in Taiwan were published in 2006 and 2009.[9,10] The current guidelines have been updated to include evidence that has accumulated over the past 5 years. This is the first guideline endorsed by the Infectious Diseases Society of Taiwan that focuses on antifungal strategies. An updated version for selection of antifungal agents for proven or probable IFDs is provided in a separate document.

Methods

This guideline is as an updated and extensively revised version of an earlier guideline published in 2009.[9] The aim of this update is to provide the rationale and recommendations for antifungal strategies according to the guide for practice guideline development.[11] The recommendations, their strength, and the quality of evidence were reviewed and discussed in a series of multidisciplinary conferences or forums during the past 5 years and are approved by the board of IDST, the Hematology Society of Taiwan (HST), and the Taiwan Society of Blood and Marrow Transplantation (TSBMT). Members of the panel represented the disciplines of the three societies and three foundations.

IDST coordinated the process of updating the guidelines. These included the development and validation phases to assure the quality of recommendations and facilitate integration of opinions from multidisciplinary professionals. In

the development phase the authors reviewed available guidelines, new primary studies, systematic reviews and local epidemiology. In addition, HST and TSBMT retrospectively analyzed IFD data in patients with hematological malignancies receiving induction chemotherapy in a teaching hospital in Taiwan[6] and hematopoietic stem cell transplantation recipients based on the Taiwan Blood and Marrow Transplantation Registry (TBMTR). The authors prepared the draft recommendations (tables and figures as in previous versions of IDST guidelines) after consensus was achieved. In the validation phase the draft was discussed by panel members from the three societies and foundations in joint meetings. The draft was revised accordingly and then sent to each society for final approval.

Three principles provided the framework for this and previous guidelines.[9,10] First, the guidelines were generated based on evidence and academic principles, rather than the regulations of the Bureau of National Health Insurance on antimicrobial usage. The majority of the recommendations are evidence-based encompassing randomized controlled clinical trials and other study results. As high-quality evidence for antifungal use are limited, in vitro data, case reports and expert opinions were incorporated as well. Second, the guidelines were based on the local epidemiology and susceptibility patterns of pathogens. The heterogeneity of the patient population and clinical practice were also taken into consideration. Third, the antimicrobial agents recommended in the guidelines are available in Taiwan.

The target patients for this guideline are adults with hematological malignancies and HSCT recipients who are at risk of developing IFDs. IFDs are classified by certainty of the diagnosis, based on host factors, clinical factors such as symptoms/signs and image findings, into proven, probable and possible IFDs for research purpose.[12] Key questions are formulated into the following major categories: risk assessment and selection of antifungal strategy; target population, regimen and duration of antifungal prophylaxis; the rationale of selecting empirical therapy versus preemptive therapy; how to integrate risk assessment, antifungal strategy and diagnostic algorithms.

For a systematic literature review, the latest guidelines of Infectious Diseases Society of America (IDSA),[13–15] the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO),[16] the Third European Conference on Infections in Leukaemia (ECIL-3),[17–19] National Comprehensive Cancer Network (NCCN),[20] National Institute for Health and Care Excellence (NICE) in Australia,[21–26] Japan[27] and Korea[28] published during 2009–2014 were collected. A literature review was performed using PubMed to identify papers published in English during January 1, 2009 to June 30, 2016. Search terms included (hematology [Title/Abstract] OR hematological malignancy [Title/Abstract] OR neutropenia [Title/Abstract] OR hematopoietic cell transplant [Title/Abstract] OR graft-versus-host diseases [Title/Abstract]) AND (fungal infection [Title/Abstract] OR antifungal [Title/Abstract]) AND (antifungal strategy [Title/Abstract] OR antifungal prophylaxis [Title/Abstract] OR empirical therapy [Title/Abstract] OR preemptive therapy [Title/Abstract] OR symptom-driven [Title/Abstract] OR diagnosis-driven [Title/Abstract]). Reports before 2009 were reviewed if they were considered to provide key evidence to support the recommendations. Related literature was added by searching references of the collected literature, manually as necessary.

The evidence was reviewed based on the GRADE method.[29–31] The panel members developed the guideline according to the process adopted by the IDSA, which systematically evaluates and explicitly states both the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong).[14,15] The strengths of recommendations are based on, but not limited to quality (certainty) of evidence. Also the panel took into consideration the balance between benefits (e.g., treatment efficacy and benefit of early intervention) and harms (e.g., potential toxicity, drug–drug interactions and negative impacts of delay in intervention; burdens, resource and cost).

To assist in implementing the guideline, this article summarizes the rationale, purpose, local epidemiology, and key recommendations. The guidelines describe how to make decisions for antifungal strategies, including prophylactic, empirical (or symptoms-driven) or preemptive (or diagnostic-driven) therapy in target patients. The recommendations are summarized in 4 tables and 3 figures with corresponding descriptions in the text and footnotes. The contents are presented in a format designed to achieve a balance between specialization and simplification and to make recommendations more understandable and more feasible for clinicians in unrelated fields. This document includes an incomplete, but essential review of local epidemiology. The references are limited to key publications not included in international guidelines.

The guideline also maps the limitation of current medical knowledge and the gaps between daily practice and for research. The guidelines are not intended nor recommended as a substitute for bedside judgment in the management of individual patients, to seek advice from qualified health care professional regarding any medical questions or conditions, or to search for updated evidence. The guidelines are published in the *Journal of Microbiology, Immunology and Infection* and are also available on the IDST website.

Recommendations

Selection of antifungal strategy

A risk-adapted and dynamic antifungal strategy is recommended, as shown in Fig. 1.[32] Risk assessment is the core concept and first element for decision making to select an antifungal strategy. IFDs are an important cause of antibacterial treatment failure in adults with hematological malignancies, particularly acute leukemia, following chemotherapy. Because of leukemia's heterogeneity, the risk for IFDs is highly variable.[33] Nucci and Anaissie suggest a risk-adapted and dynamic antifungal strategy with strong emphasis on pretreatment and day-15 posttreatment to allow earlier and more individualized interventions.[34] Pretreatment risks for IFDs in daily practice are evaluated based on four perspectives: host factors, treatment factors, other co-morbidities or conditions, and patient

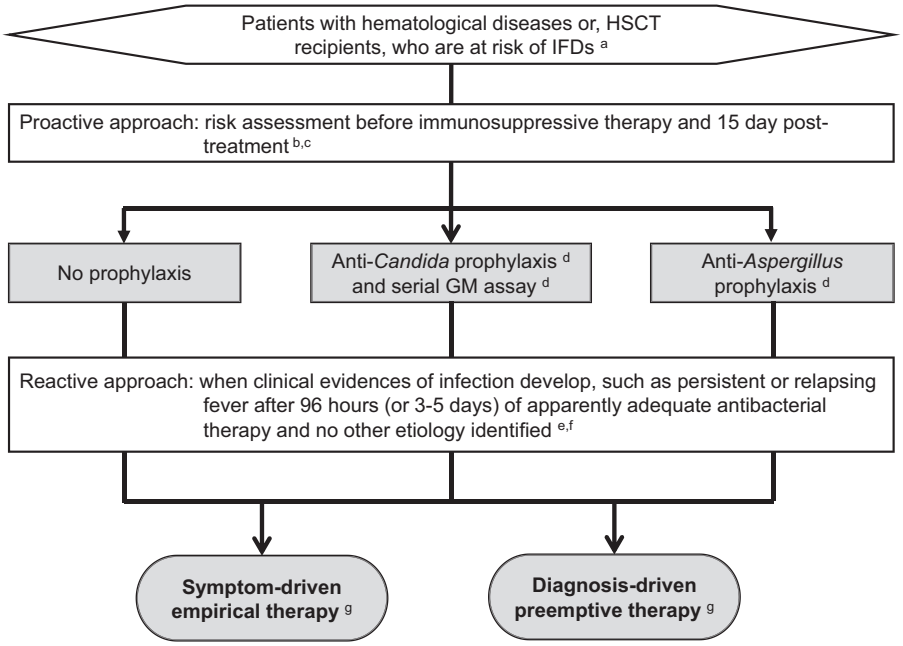

Figure 1. Risk-adapted and dynamic algorithm to select antifungal strategy for patients with hematological diseases or HSCT recipients, who are at risk of IFDs. Antifungal strategies include prophylaxis, symptom-driven (or empirical) therapy, diagnosis-driven (or pre-emptive) therapy, and pathogen-targeted (or definitive) therapy. *Footnote*: [a]Because of the heterogeneity of patients with hematological diseases, even acute leukemia or HSCT recipients, the risk for IFDs is highly variable and results from interactions between primary diseases, immunogenetic factors, net state of immunosuppression, organ dysfunction, and exposure to opportunistic fungi. Risk factors to be considered are described in Table 1. Well-known high-risk patient populations include: 1. Acute leukemia or myelodysplastic syndrome patients receiving chemotherapy. 2. Hematopoietic stem cell transplantation recipients. 3. Prolonged use of steroid (>0.3 mg/kg/d for 60 days). 4. Use of T-cell immunosuppressants (cyclosporine A, tumor necrosis factor-α blockers, monoclonal antibodies, nucleotide analogues, etc. within 90 days). 5. Inherited severe immunodeficiency. [b]The evidence-to-decision framework of determining antifungal strategy is described in Table 2. [c]In addition to select antimicrobial prophylaxis strategy, the patients and their family members/main care givers should be educated for hand cleaning, personal hygiene, and food safety. Other measures to prevent exposure are also described in Table 1. [d]Selection of prophylactic strategy should be individualized at each hospital, or, even for each patient, after considering factors described in Fig. 2. [e]Evidences of infection vary by focus of infection, etiology, host factors and healthcare factors. Duration of fever are suggested based on clinical studies, but individual judgment based all parameters are the key. [f]Not all infections in high-risk patients for IFDs are due to fungal pathogens; distinguishing presumed fungal infection from bacterial, mycobacterial or viral infection is still important. [g]Please refer to Taiwan 2016 guideline for use of antifungal agents[32] for the choice of drugs. Prior use of antifungal agents (including during prophylaxis) should be taken into consideration in choosing antifungal agents. When empirical therapy is instituted, aggressive diagnostic workups are still required. Even after starting empirical therapy, the diagnosis of IFDs should still be regularly reviewed; discontinuation, de-escalation or revision of antifungal drugs will be considered if the diagnosis is revised.

exposure to opportunistic fungi.[33,34] Factors in the four perspectives are further illustrated in Table 1.[33,35–43] Accordingly, patients are stratified into high, intermediate, or low risk for IFDs; risk-adapted antifungal strategies,[34,44] including prophylaxis, preemptive or empiric therapy, to be applied within an evidence-to-decision framework (Table 2).

Thus, it is important to integrate multiple risk factors into risk scores in order to guide decision making. For example, scores are based on 4 independent variables of invasive mold diseases (IMD) in patients with hematological malignancies and HSCT recipients (prior IMD), 4 points; prolonged neutropenia, 4 points; malignancy status, 3 points; lymphocytopenia or lymphocyte dysfunction in allogeneic HSCT recipients, 2 points; a risk score of <6 discriminated patients with low (<1%) versus higher incidence rates (>5%) of IMD.[45] This objective, weighted risk score for IMD is designed to facilitate "screening-out" of low risk patients less likely to benefit from intensive diagnostic monitoring or anti-mold prophylaxis.

Non-pharmacological measures to modify risk factors continue to be the cornerstone for better outcomes by preventing IFDs. For example, instead of using highly immunosuppressive chemotherapy, novel targeted therapies, that can now achieve higher rates of sustained remission for poor-risk patients with less adverse effects, and offer the best promise for reducing the burden of IFDs.[34] Furthermore, implementing protective measures from acquisition, colonization and subsequent invasion/infection of pathogens is important before applying any antifungal strategies. Hand hygiene is as effective for preventing cross transmission of fungi as it is for bacteria.

Table 1 Summary of risk factors for invasive fungal diseases in patients with hematological diseases or hematopoietic stem cell transplantation recipients.[33,35–43]

Category	Risk factors[a]	Low/intermediate risk	High risk
Host-related	Type of underlying hematological diseases	Lymphoma, childhood ALL[b] Myeloma, CLL	AML
	Status of underlying hematological diseases	Complete or partial remission	Refractory/progressive, relapse
	Host fitness for standard therapy	Fit	unfit, or frail
	Age		>40 years
	Immunogenetic status		Toll-like receptors polymorphism, C-type lectin receptor polymorphism, Mannose binding lectin polymorphism Plasminogen polymorphism
Treatment-related	leukemia resistance	high probability of achieving complete remission	low probability of achieving complete remission
	anticipated treatment-related toxicity such as neutropenia, mucositis	Neutrophils 100–500/mL < 3 weeks Lymphocytes < 500/mL + antibiotics	Neutrophils < 100/mL > 3 weeks Neutrophils < 500/mL > 5 weeks
	steroid- or T-cell suppressors induced immunosuppression		Corticosteroids > 1 mg/kg and neutrophils < 100/mL > 1 week Corticosteroids > 2 mg/kg > 2 week High-dose Ara-C + fludarabine[d] (FLAG) Alemtuzumab Anti-thymocyte globulin
	HSCT	PBSCT Autologous HSCT TBI,[c] allogeneic matched sibling donor HSCT	Allogeneic Matched unrelated donor, mismatched donor, haploidentical HSCT; Cord blood transplantation; CD34-selected or T-cell depleted graft
	GVHD or graft rejection in HSCT		Grade II/III GVHD Extensive chronic GVHD
Other co-morbidity or conditions	Other co-morbidity	Diabetes, poorly controlled Renal impairment Metabolic acidosis Trauma or burns, severe	Iron overload Use of deferosamine
	Prior respiratory disease in HSCT		CMV pneumonitis
Exposure to pathogenic fungi or colonization	Colonization status[e] and factors interfere ecology	Intermediate high: colonized by *Candida* > one site or heavy at one site + neutrophils < 500/mL > 3 weeks	*Candida tropicalis* in allogeneic unrelated or mismatched donor HSCT Nose or lower respiratory tract colonization with *Aspergillus flavus* or *A. fumigates*

(*continued on next page*)

Table 1 (*continued*)

Category	Risk factors[a]	Low/intermediate risk	High risk
	Others	Intermediate: No HEPA filtered air during HSCT Current user of tobacco or marijuana	Profession with likely repeated exposure to fungal spores: patient works as a farmer, mason, carpenter/construction or has outdoor work with likely spore exposures. On-going construction at home, nearby community or patient was admitted to hospital room in a ward or building with ongoing construction Contaminated food or spices
	Geo-climate		Environmental spore counts

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; HSCT = hematopoietic stem cell transplantation; MDS = myelodysplastic syndrome; GVHD = graft versus-host disease; TBI, total body irradiation.

[a] Suggest consult hematologists and infectious diseases physicians for risk assessment. Factors associated with invasive fungal diseases (IFD) vary by fungal pathogens, such as *Candida*, *Aspergillus*, *Mucormycetes* and others.

[b] Risk of IFD in pediatric patients with ALL is low except for *Pneumocystis carinii* pneumonia.

[c] Total body irradiation (TBI) is a potent cause of gastrointestinal damage, the probable cause for its identification as a risk factor for higher rate of IFD in HSCT.

[d] Fludarabine is a powerful immunosuppressant with a prolonged length of effect (months) on lymphopoiesis and a medium-term (3—5 weeks) myelosuppression.

[e] Prior colonization is almost a prerequisite of invasive candidiasis and is predictive of subsequent infection. In addition, risk of invasive candidiasis may very by amount of colonization (heavily colonization), number of anatomic sites colonized (one, two or more), site of colonized (rectal versus respiratory), and *Candida* species (*Candida tropicalis* versus *Candida albicans*). Prior bacteremia and/or prior use of broad spectrum antibacterial agents are associated with increased risk of IFD. The probable reasons include sepsis induced immunosuppression and alteration of the natural gastrointestinal flora and resulting fungal colonization, which, in turn, increases the risk for IFD.

Advice to avoid the use of contaminated foodstuffs, notably pepper, other spices, unpasteurized beer, and 'alternative' unlicensed medications is also critical, because fungal outbreaks have been traced to such behaviors. Efforts to prevent air-bone *Aspergillus* infection, such as caring for very high risk patients in protective rooms with high-efficiency particulate air (HEPA)-filtered air under positive pressure or laminar airflow, or avoiding exposure to gardening or reconstruction without protection, are also useful.

Awareness of fungal epidemiology at both a population wide and local level remains an important consideration. Since the introduction of fluconazole and itraconazole prophylaxis or early therapy in high-risk patients and implementation of serum galactomannan antigen assay, there has been a change in epidemiology. *Aspergillus* species have replaced *Candida* species as the most common fungal pathogen.[6] There is also considerable variability in the incidence and etiology of IFDs between sites of care. This will impact the decision to use prophylaxis and subsequent choice of agent. Furthermore, the risk of IFDs in patients receiving new targeted cancer therapy is not well characterized. Thus, it is recommended that antifungal strategies should be determined at each hospital based on local epidemiology. The importance of an individualized approach is emphasized because of the heterogeneity of patient populations (Figs. 1 and 2).

Prophylactic strategy

There is a strong argument for the use of antifungal prophylaxis in high-risk patients given the significant mortality associated with invasive fungal disease, the difficulty in identifying these infections, and the availability of safe and well-tolerated prophylactic medications. Clinical decisions about which patients should receive prophylaxis and the choice of antifungal agent should be guided by risk stratification, knowledge of local fungal epidemiology, the efficacy and tolerability profile of available agents, and estimates such as number needed to treat and number needed to harm. There have been substantial changes in practice since the 2009 guidelines were published. These include the availability of new medications and/or formulations, and a focus on refining and simplifying patient risk stratification. Used in context, these guidelines aim to assist clinicians in providing optimal preventive care to these vulnerable patients.

Prophylactic strategies for, patients without any symptoms or signs of infection, need to carefully consider the risks for fungal infections in very high risk patients. These include those with neutropenia after induction chemotherapy, acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS) and allogeneic hematopoietic stem-cell transplantation (HSCT) recipients. Targeted prophylaxis has been shown to reduce the rate of IFD and

Table 2 The evidence-to-decision framework of determining antifungal strategy.

Category	Remarks
Assess risk	Assess risk of invasive fungal diseases (IFDs) before immunosuppressive therapy (factors described in Table 1). Selection of immunosuppressive agents should take into account of risk of infection as well and implement prevention measures proactively. Assess at 15 days after myelosuppressive therapy in patients with acute leukemia. Delay in recovery of marrow might be the early sign of new infection or inadequate control of infection. Timing of re-assess the risk of infection varies by regimen. Assess when patients have any evidence of infection.
Be vigilant	Be aware of the risk and the occurrence of IFDs. Be aware of the potential fungal pathogens and their usual in vitro susceptibility pattern and manage accordingly. Be aware of comorbidities which increase the risk of IFDs and drug-related adverse reactions.
Costs-benefits balance	Take local epidemiology into account to decrease the number-need-to-treat for prophylaxis or the number-need-to-test to achieve better cost-effectiveness ratio. Consider both economic and non-economic perspectives of costs or benefits. The latter includes adverse events of antifungal agents, survival, quality of life, psychosocial, etc. Consider both direct and indirect costs. The latter includes drug-related direct toxicity and toxicity secondary to drug—drug interaction. Consider balance between pharmacological interventions for underlying diseases as well as for antifungal therapy and their interactions. Accessibility to health care and hospitalization. Availability, accessibility, performance, and turning-around time of diagnostic tools

improve overall survival in some settings.[46,47] The problem with this approach is that it may impair the yields of diagnostic tests and complicate further management of breakthrough IFD.[48]

Selection of antifungal agents for prophylaxis

Comprehensive head-to-head comparison among different antifungal agents and placebo for prophylaxis is not possible. Therefore, novel statistical methods, such as network meta-analysis, can be conducted to estimate the relative effectiveness of each strategy in high risk patients.[49] In general, IFD prophylaxis has a positive effect on IFI risk reduction, but its effect on all-cause mortality is not as pronounced. This indicates that the underlying disease remains the key factor for survival.[49] Furthermore, antifungal prophylaxis for higher-risk diseases does not always cost more, and does not always do better.[49] It is therefore recommended that country-specific cost-effectiveness of antifungal prophylaxis be required and local epidemiology be the key determinant.[50] Most guidelines recommend primary antifungal prophylaxis for patients above a risk threshold of 20%.[21]

Considerations that may influence the decision-making process when choosing between specific agents are included in Table 2. These include efficacy, tolerability and bioavailability, local IFD epidemiology (yeast or molds), adverse effects, and potential drug—drug interaction profile, availability of expertise and diagnostic tools for early diagnosis of breakthrough IFD, and drug costs. Accordingly, the recommendations for the antifungal agents used for prophylaxis are listed in Table 3, with reference to at-risk patient groups according to different underlying diseases and conditions. Despite the limited efficacy of nystatin, it remains recommended in this guideline due to its minimal systemic effects, low toxicities and cost.[51] Prophylactic fluconazole may be a worthwhile alternative for mold-active prophylaxis in allogeneic HSCT[46] in centers practicing early diagnostics-driven therapy.[26] Mold-active azoles, and probably echinocandins, are proven to be effective in preventing IFDs in certain high-risk conditions,[47,52–54] but their use still should be considered for individual patients.

Of note, all of the mold-active azoles adversely interact with immunomodulatory and antineoplastic drugs[55] and compromise the performance of diagnostic biomarkers.[48] Consulting physicians and the patients/main caregivers should be very alert to the occurrence of IFDs in patients who are at high risk, but not receiving antifungal prophylaxis. They should implement either biomarker-driven preemptive therapy or empirical therapy. According to a recent study there was no difference in outcomes of patients who received integrated diagnostics in the absence of antifungal prophylaxis and those who received primary anti-mold prophylaxis.[56]

Secondary prophylaxis aims at preventing relapse of a previous IFD, or the onset of another IFD, during a new at-risk period. This is defined as either a prolonged neutropenic phase, usually chemotherapy induced, or a phase of severe immunosuppression, mainly after allogeneic HSCT.[18] For the drug selection, no specific recommendations were formulated, other than that the choice of drug and dose be based on the causative fungal pathogen of the previous IFD and the previous response to antifungal agents (as in Table 3).[57]

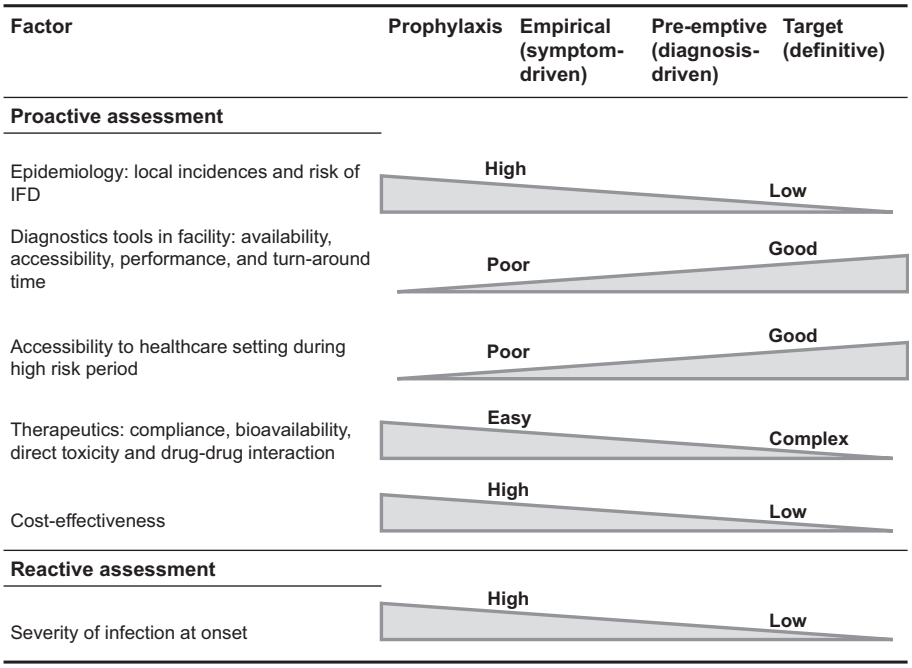

Figure 2. Selection of antifungal strategy for invasive fungal diseases: prophylaxis, empirical versus preemptive therapy. Preemptive or diagnostic-driven strategy is increasingly favored than empirical strategy. However, decision should be made individualized according to, but not limited to, the following hospital factors or patient factors.

Symptom-driven, or empirical strategy

The severity and extent of neutropenia are considered major risk factors for IFDs in patients with hematological malignancies after intensive myelosuppressive chemotherapy. Early intervention should be based on clinical presentation and risk assessment in high-risk patients (that is, symptom-driven or empirical therapy) rather than waiting for microbiological or histopathological confirmation for definitive therapy. This continues to be the standard of care for the past two decades. It is usually given in the setting of prolonged febrile neutropenia in patients with hematological malignancies after intensive myelosuppressive chemotherapy after 96 h (3—5 days) of apparently adequate antibacterial therapy without any other etiology identified.[11] Major progress has been made by the advent of new antifungals since the late 1990s. Lipid-based amphotericin B, third-generation azoles and the introduction of echinocandins allow a safer and effective early intervention of IFDs.

Being alert and integrating aggressive diagnostic approaches with prompt antifungal therapy are essential for patient survival. Of note, an empirical strategy does not diminish the importance of a diagnostic approach. Every effort should be made to determine whether IFD exists before empirical therapy is started. This includes biopsy of lesions, radiographs of the chest and sinuses, stains and cultures, CT of the chest and abdomen, and nasal endoscopy or bronchoscopy if indicated.[13] The empirical decision to start a drug is not as difficult as the decision to discontinue its use. Much of the evaluation to initiate antifungal therapy aids decisions about when to stop antifungal treatment or whether secondary prophylaxis is indicated during the subsequent at-risk period.

The difficulty with empiric antifungal therapy for clinical scenarios described above is that it can lead to overtreatment, exposing patients to unnecessary antifungal toxicities and increased costs.[13,26] There is a need for better risk stratification or new antifungal strategies. Diagnosis-driven or preemptive strategies, have been proposed to cope with this dilemma. Nevertheless empirical therapy continues to be strongly recommended as a reasonable, pragmatic approach to limit the ominous threat of IFDs, particularly for high-risk patients with moderate or severe illness or severely immunocompromised status.

There is no consensus regarding the indications for empirical therapy in high-risk patients other than those with hematological malignancies following intense myelosuppressive chemotherapy. In addition, there is inadequate evidence to support recommendations for febrile neutropenic patients if they are already on antifungal prophylaxis or receiving empirical therapy.

Diagnostic-driven, or preemptive strategy

Diagnostic-driven, or preemptive strategies, are increasingly favored over empirical therapy because of the concerns of overuse of empirical therapy described above. Preemptive therapy is administrated when radiographic signs and/or laboratory findings are suggestive of IFD (that is, probable IFDs) without definite histopathological or mycologic identification (that is, proven IFDs). With the advancement in biomarkers and molecular diagnostics, diagnoses can now be made earlier and unnecessary use of

Table 3 Recommendations for antifungal agent usage in patients with hematological diseases or hematopoietic stem cell transplantation recipients by different strategy.

Patient population or antifungal strategy	Primary	Alternative[a]	Comments
Primary prophylaxis			1. Strategies to reduce risk of invasive fungal diseases through modifying risk factors such as control of underlying diseases or conditions, environmental control to reduce exposure to fungi, and patient education for personal hygiene and food safety are important before adapting prophylactic strategy. 2. Prophylactic use of anti-mold agents reduces the yields of galactomannan antigen assay and molecular diagnostics. 3. Prophylactic strategy may increase the uncertainty or difficulty of managing subsequent fungal infections 4. Please refer to Fig. 1 for selecting antifungal strategy 5. If the risk of invasive mold diseases is low, may use fluconazole as antifungal prophylaxis and combine with a mould-directed diagnostic approach. 6. Duration of therapy is based on recovery from neutropenia or immunosuppression.
AML and MDS patients receiving induction chemotherapy[b]	Nystatin (S/L)	Posaconazole (S/H)[c] Itraconazole (W/H)[d] Fluconazole 50—400 mg (W/H) AmB-d (W/H)	Clinical trials for fluconazole showed various results.
Autologous HSCT, initial neutropenic phase	Nystatin (S/L) Fluconazole (S/H)	Micafungin iv (W/H)	One may consider antifungal prophylaxis when patient has mucositis if initially no systemic prophylaxis is given. For echinocandin, data are available for micafungin only.
Allogeneic HSCT, initial neutropenic phase	Nystatin (S/L) Fluconazole 400 mg iv or po (S/H) Micafungin 50 mg (W/H)	Voriconazole 200 mg (4 mg/kg) bid po (W/H) Itraconazole (W/H) AmB-d (W/H)	
Allogeneic HSCT, GVHD phase	Nystatin (S/L) Posaconazole (S/H) Voriconazole (S/H)	Itraconazole (W/H)[d] Fluconazole (W/H) AmB-d (W/H)	Prophylactic use of anti-mold agents is recommended in patients with severe GVHD under treatment with high dose steroid or equivalent immunosuppressants The usually recommended duration of an antifungal primary prophylaxis in allogeneic HSCT is 90—100 days. It is usually accepted that primary prophylaxis should be continued beyond day 100 in case of persisting GVHD and/or ongoing immunosuppressive therapies at this time.
Allogeneic HSCT within 180 days, and no neutropenia or GVHD noted	Nystatin (S/L)	Fluconazole (S/H) Voriconazole (W/H) Itraconazole (W/H)[d]	Prophylactic use of fluconazole, itraconazole, or voriconazole may consider extension to day 100 after HSCT, or day 180 after HSCT in selected high risk patients (such as high dose steroid use, T cell depleted graft, etc).

(*continued on next page*)

Table 3 (*continued*)

Patient population or antifungal strategy	Primary	Alternative[a]	Comments
Secondary prophylaxis			
Patients with prior history of IFDs	Depends on etiology of prior infection	Depends on etiology of prior infection	No standard approaches due to lack of evidences. Second prophylaxis is strongly recommended in patients with previously defined IFD during subsequent at-risk periods (S/L).
Empirical therapy			Please refer to Fig. 1 for selecting antifungal strategy Initiation or modification of an antifungal regimen for patients with persist febrile neutropenia (generally 4—7 days in duration) that is without a known source and is unresponsive to appropriate antibiotics
	AmB-d 0.5—1.0 mg/kg iv (S/M) Caspofungin 50 mg iv (S/H) L-AmB 3 mg/kg iv (S/H)	Voriconazole po (S/H) Itraconazole (S/L)[d] Micafungin 100 mg iv (S/H)	AmB-d is strongly recommended for high-risk patients in the absence of risk factors for renal toxicity (for example, impaired renal function at baseline, nephrotoxic comedication including cyclosporin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity); but weakly recommended for patients with impaired renal functions or in the presence of aforementioned risk factors of renal toxicities.
Diagnostic-driven (or preemptive) therapy			Please refer to Fig. 1 for selecting antifungal strategy Regimens please refer to Taiwan 2016 guideline for use of antifungal agents,[32] according to etiologies

Abbreviations: AmB-d = amphotericin B deoxycholate; iv = intravenous; po = orally; L-AmB = liposomal amphotericin B; IFD = invasive fungal diseases; HSCT = hematopoietic stem cell transplantation; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; GVHD = graft versus-host disease; N/A = not available.

Grading of recommendation and evidence: S/H, strong recommendation, high-quality evidence; S/M, strong recommendation, moderate-quality evidence; S/L, strong recommendation, low-quality evidence; S/V, strong recommendation, very low-quality evidence; W/H, weak recommendation, high-quality evidence; W/M, weak recommendation, moderate-quality evidence; W/L, weak recommendation, low-quality evidence; W/V, weak recommendation, very low-quality evidence.

[a] Alternative agents are considered in the following concerns or conditions: allergy, pharmacology/pharmacokinetics, local resistance profiles of most common fungal pathogens, intolerant of or refractory to primary agent.

[b] Primary prophylaxis is not routinely applied to selected patient population or clinical situations, certain regimens with good evidence for prophylaxis use such as oral posaconazole are included as alternative agents instead of primary agents.

[c] Posaconazole delayed-release tablets 300 mg twice a day on the first day and then, 300 mg once a day, starting on the second day. Posaconazole oral suspension 200 mg orally three times daily and taken with greasy food to assure absorption. Be aware of breakthrough fungal infection during posaconazole prophylaxis due to inadequate drug level secondary to oral bioavailability in patients with mucositis or diarrhea, or drug—drug interaction with proton pump inhibitors, etc.

[d] Itraconazole 200 mg iv daily, followed by oral solution 200 mg orally twice a day. Adequate dosing is necessary to ensure an effect. The bioavailability of itraconazole capsure is so low that even 800 mg/day alone will not achieve the necessary trough levels in more than 50% of the patients within the first week of prophylaxis.

empiric therapy can be curtailed.[26,58—61] Compared with empiric therapy, the diagnostic-driven approach did not jeopardize patient outcomes in randomized clinical trials and is likely to be cost-saving due to a reduced incidence of adverse events and decreased use of empirical antifungal therapy.[60] Preemptive strategies (biomarker-driven targeting prophylaxis) also provide an alternative to universal mold-active prophylaxis in at-risk patients.

The diagnostic-driven approach, however, is limited to hospitals that have the appropriate laboratory infrastructure and a reasonable turnaround time. In addition, diagnostic biomarkers need to be interpreted appropriately. The diagnostic accuracy of the galactomannan antigen assay, β-D-glucan assay, and molecular diagnostic tests, published in the literature, are mostly, generated based on active surveillance. Samples were collected frequently

(daily or at least twice weekly) in untreated, very high risk patients. They were mostly patients with hematological malignancies with neutropenia following chemotherapy and HCST recipients with severe GVHD.[62] In addition, the analysis of the data was limited to patients with proven or probable IFDs. In contrast, the majority of patients cared for in daily practice are treated by a decision-driven diagnostic approach. The new tests are usually performed on demand and critical decisions are usually made based on a single data point.

For these reasons decisions concerning the choice of preemptive or empirical strategies should be individualized according to hospital or patient factors (Fig. 2). These include feasibility, accessibility and turn-around time of diagnostics, severity of infection, local epidemiology and risk of IFD, adverse effects and drug—drug interaction of specific drugs, and pharmaco-economic considerations. An empirical strategy is favored for patients with severe illness. Preemptive strategy is favored if the risk (or incidence) of IFD is low, based on local or literature-reported epidemiology; and diagnostics tools for early detection of IFDs to initiate antifungal agent and/or selecting antifungal agents that are available and easily accessible. The results of diagnostic tests need to be available within a short period of time. These include high-resolution CT scan, fungal antigen assays including galactomannan antigen assay and molecular diagnosis methods. We need to also consider the cost-effectiveness of the strategy, considering that the costs saved by the decreased use of antifungals counter-balanced by the increased costs of the diagnostic procedures.

Because of the limited evidence and the heterogeneity of clinical scenarios, no recommendations are provided in this guideline about type and timing of noninvasive diagnostic procedures, choice and time to start of the antifungal therapy in the absence of specific clinical information and assessment of each patient.

Selection of antifungal agents for empirical or preemptive strategies

Factors influencing the choice of antifungal agents include four dimensions, patient, clinical scenarios, pathogen, and pharmacological. In addition, decisions need to be based on the consideration of interactions between each dimension. These include, but are not limited to: underlying diseases/status, co-morbidities, severity of the infection, focus of infection, the most likely pathogen, antifungal susceptibility, prior exposure to antifungal agents, antifungal spectrum, potential drug—drug interactions, undesirable effects including allergy, intolerance, emergence of resistance, and pharmacokinetic and pharmacodynamic factors. When there are ample options for antifungal agents, relative toxicity drug interactions and costs become the major concerns.

Randomized controlled trials (RCTs) provide the most reliable estimates of therapeutic efficacy. However, not all treatments are compared in RCTs. This makes it problematic to judge whether one drug is superior to another. Mixed treatment comparisons (MTCs) are conducted to estimate the comparative effects across a range of available therapeutic options.[11] For empirical therapy, caspofungin has proven to be superior to amphotericin B, liposomal amphotericin B, amphotericin B lipid complex and voriconazole for survival. However no agents have been shown superiority for response to treatment.[11] In MTCs, no differences were identified between pre-emptive and empirical strategies in relation to mortality. For diagnostic-driven or directed therapy voriconazole was found to be superior to amphotericin B for overall survival. Both voriconazole and liposomal amphotericin B were shown to be superior to amphotericin B or amphotericin B colloidal dispersion on outcome.[11]

Antifungal stewardship

The current recommendations were prepared in conjunction with the antimicrobial stewardship program in Taiwan. To improve patient safety, optimal use of antimicrobial agents, and prevent adverse reactions including drug resistance, a national antimicrobial stewardship program sponsored by Taiwan CDC was undertaken during 2013—2015. This program emphasizes five components for improvement of antimicrobial use: diagnosis, drug, dosage, de-escalation and duration. Special emphasis in this guideline is placed on accurate, diagnosis. Confirmation of etiology and site of infection helps guide the optimal choice of antifungal agent, dosage, duration of therapy, and the necessity for secondary antifungal prophylaxis during the subsequent chemotherapy or HSCT. Furthermore, careful evaluation is needed to exclude the presence of an active IFD before initiating primary antifungal prophylaxis. This requires a careful history of the presence of IMD during prior chemotherapy and the need to initiate secondary anti-mold prophylaxis. This guideline encourages diagnostic-driven or preemptive strategies and de-escalation of empirical therapy when no longer needed.

Health economic consideration

To optimize the utilization of limited resources in healthcare system, health economic analysis, which aims at demonstrating the effectiveness of medical innovations, plays a more important role in the decision-making process among different stakeholders.[63,64] It should be important to the medical academic societies as well, because social justice in resource allocation is also an essential part for medical professionalism.[65]

Cost-effectiveness analysis is the most widely used economic evaluation to assess novel medical interventions.[64] For primary antifungal prophylaxis in hematological diseases the results of analysis vary by country even under similar scenarios,[66] as shown in Fig. 3. The possible explanations include differences in the baseline incidence of IFD and costs of antifungal agents, diagnosis, hospitalization and supportive care. Antifungal prophylaxis is most likely cost-effective when limited to very high risk populations (with increased incidence). Furthermore, implementing results from network meta-analysis into built economic models is helpful to overcome the challenges in conducting cost-effective analysis in complicated comparison in using antifungal agents.[49]

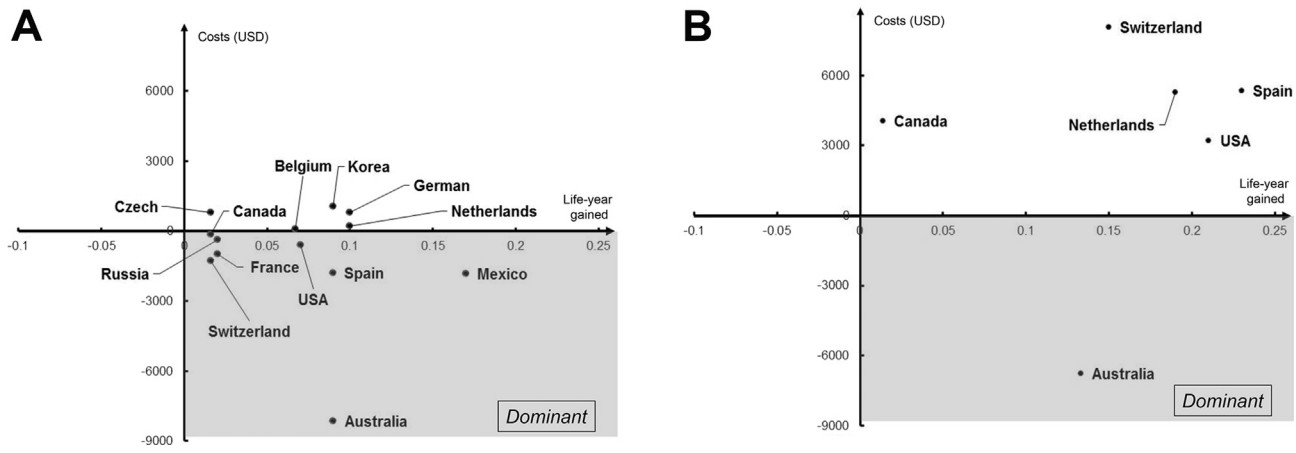

Figure 3. Plotted cost-effective plane for using posaconazole as anti-fungal prophylaxis in different countries. (A). In acute myeloid leukemia patients receiving induction chemotherapy; (B). In allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. Adapted from the article by Lyseng-Williamson.[66]

In the recent IDSA guidelines, the strength of the recommendations is also influenced by disease burden, resource utilization, costs, patients' values and preferences.[14,15] The number needed to treat (NNT) and number needed to harm (NNTH) — as well as an individual patient's IFD risk — is also a useful concept to guide clinical decision making. Current expert opinion favors an NNT of around 20 for optimal benefit.[21] If NNTH is smaller than NNT, a prophylactic strategy is not appropriate. When applying this concept locally, clinicians need to be cognizant of deficiencies in local diagnostics. These can impact the background rate of IFD detection, which may falsely lower or elevate NNT. The NNT for IFDs in several critical hematological scenarios are estimated in Table 4,[6,47,67–69] according to published epidemiological data in Taiwan.[6,68,69]

Table 4 Estimated numbers needed to treat on the basis of epidemiological data in patients with hematological malignancies in Taiwan.

Patient population	Study design	Study period	Study number	IFD category	IFD incidence	NNT	Reference
Adult AML[6]	Prospective,	2004—2009	298 patients	Proven/Probable	10.7%	12[a]	Tang et al.[6]
Induction chemotherapy	Single center			Proven/Probable/Possible	34.6%	3[a]	
Adult AML[68]	Retrospective,	2010—2014	39 patients	Proven/Probable	17.9%	6[a]	Yang et al.[68]
Induction chemotherapy	Single center						
Pediatric AML[69]	Prospective,	2010—2012		Proven/Probable			Yeh et al.[69]
Induction chemotherapy	Single center		28 courses		17.9%	6	
Post-remission high dose			76 courses		7.9%	13	
Post-remission modest dose			56 courses		1.8%	56	
Pediatric ALL[69]	Prospective,	2010—2012		Proven/Probable			Yeh et al.[69]
Induction chemotherapy	Single center		62 courses		14.5%	7	
Consolidation chemotherapy			59 courses		0%	NA	
Re-induction chemotherapy			59 courses		1.7%	59	

Abbreviations: IFD, invasive fungal diseases; NNT, number needed to treat.
[a] NNT is calculated on the inverse of the absolute risk reduction with antifungal prophylaxis,[67] and the incidence of IFDs with antifungal prophylaxis is based on the data from the study by Cornely et al.[47]

Conclusion

Clinical guidelines are designed to improve the quality and appropriateness of care, cost-effectiveness, and to serve as educational tools.[11] Practice guidelines, however, can never be a substitute for clinical judgment. Clinical discretion is still of the utmost importance in the application of a guideline to individual patients. No guideline can ever be specific enough to be applied in all situations.[11] With this guideline, we aim to provide physicians with tools to navigate the maze of approaches to suspect and diagnose IFDs by means of an integrated care pathway of rational patient management. These algorithms for clinical pathways will inevitably vary in detail for different scenarios. Implementation of evidence-based guidelines for the treatment of IFD requires collaboration among numerous clinical and laboratory services, as partners in patient care. We therefore recommend that multidisciplinary teams in each institution develop explicit agreements on the minimum requirements for effective management.[70] The integrated care pathways presented here constitute an objective instrument to allow regular audits for recognizing opportunities to change practice and identify and correct weaknesses.[70]

Author contributions

YC Chen, coordinate and chair the review and guideline development process, prepare the manuscript; BS Ko, review evidence, content development and prepare the manuscript; HC Kung, review evidence and content development; Chen YT, review evidence and content development; other authors involve in content development and critical review of the manuscript.

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