Expert Consensus

Consensus for antifungal stewardship in China (2024 edition)

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Background: Invasive fungal disease (IFD) has become a serious threat to human health in China and around the world, with high mortality and morbidity. Currently, the misdiagnosis rate of IFD is extremely high, compounded with the low quality of prescription antifungals and the high incidence of adverse events associated with IFD treatment, resulting in lengthy hospitalization, low clinical response, and high disease burden, which have become serious challenges in clinical practice. Antifungal stewardship (AFS) can not only significantly increase the early diagnosis rate of IFD, reduce inappropriate utilization of antifungal drugs, improve patient prognosis, but can also improve therapeutic safety and reduce healthcare expenses. Thus, it is urgent to identify key AFS metrics suitable for China's current situation.

Methods: Based on metrics recommended by international AFS consensuses, combined with the current situation of China and the clinical experience of authoritative experts in various fields, several metrics were selected, and experts in the fields of respiratory diseases, hematology, intensive care units (ICUs), dermatology, infectious diseases, microbiology laboratory and pharmacy were invited to assess AFS metrics by the Delphi method. Consensus was considered to be reached with an agreement level of ≥80% for the metric.

Results: Consensus was reached for 24 metrics, including right patient metrics (n=4), right time metrics (n=3), and right use metrics (n=17). Right use metrics were further subdivided into drug choice (n=8), drug dosage (n=4), drug de-escalation (n=1), drug duration (n=2), and drug consumption (n=2) metrics. Forty-six authoritative experts assessed and reviewed the above metrics, and a consensus was reached with a final agreement level of ≥80% for 22 metrics.

Conclusions: This consensus is the first to propose a set of AFS metrics suitable for China, which helps to establish AFS standards in China and is also the first AFS consensus in Asia, and may improve the standard of clinical diagnosis and treatment of IFD, and guide hospitals to implement AFS, ultimately promoting the rational use of antifungal drugs and improving patient prognosis.

Keywords: Antifungal stewardship (AFS); metrics; invasive fungal disease (IFD); Delphi; consensus

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Introduction

Background

Antifungal stewardship (AFS) is an intervention approach that improves the quality of antifungal drug use in patients with invasive fungal disease (IFD), with three implications: (I) improvement of diagnostic and monitoring criteria, and reasonable selection of appropriate antifungal drugs, administration time and therapeutic dose according to accurate evaluations; (II) reduction of adverse events as much as possible according to the individual situation of patients and the toxic and side effects of drugs; (III) helping the health care system implement an overall plan to reduce health care costs. The principles of AFS can be summarized as the 3Rs, namely: the right patient (selecting the right patient via early diagnosis of IFD), the right time (selecting the right treatment time by stratified diagnosis of IFD), and the right use of antifungals (selecting the right drug, dose and treatment duration, with appropriate drug de-escalation and drug consumption monitoring to achieve appropriate use of antifungal drugs). Evidence suggests that IFD incidence in China is steadily increasing, coupled with high clinical missed diagnosis/misdiagnosis (86.1%) (1) and high mortality (52.5–100%). In addition, the rate of irrational antifungal use (44%) (2), the incidence of treatment-related adverse events (29.0%) (3), and the rate of drug interactions (88%) (4) are all high, resulting in long average hospital stay, high intensive care units (ICUs) occupancy rate, high readmission rate, high medical costs, low success rate of treatment, and heavy disease burden on the patients (5). Therefore, IFD has become a major infectious disease threatening public health in China and even around the world.

Highlight box

Key recommendations

- The principles of antifungal stewardship (AFS) can be summarized as the 3Rs, namely: the right patient, the right time, and the right use of antifungal drugs.

What was recommended and what is new?

- Eight right use metrics are referred to the international Delphi survey published in *J Antimicrob Chemother* including four of the drug choice metrics (i.e., appropriate indications, refer to the antimicrobial spectra, follow evidence-based guidelines, and discuss with the appropriate management team), one of the drug dosage metrics (i.e., select appropriate loading and maintenance doses), and all of the drug de-escalation and drug consumption metrics.
- This consensus proposes for the first time a set of AFS metrics suitable for China, two-thirds of which were modified or newly added from the results of the international Delphi survey, including all the right patient metrics, the right time metrics, and all the drug duration metrics in the right use, as well as the remaining four drug choice metrics and three drug dosage metrics.

What is the implication, and what should change now?

- The proposal of these 24 metrics may provide a reference basis for the management and monitoring of invasive fungal disease (IFD) in medical and healthcare institutions, improve the standard of clinical diagnosis and treatment of IFD, promote the rational use of antifungals and improve patient prognosis. Medical and healthcare institutions should select the right patient (via early diagnosis of IFD), at the right treatment time (via stratified diagnosis of IFD), and ensure the right use of antifungal drugs, including choosing the right drug with the right dosage, with appropriate drug duration, drug de-escalation and drug consumption monitoring.

Rationale and knowledge gap

The National Health Commission issued the Notice on the Establishment of a National Fungal Disease Surveillance Network in 2019 and the National Action Plan for Combating Microbial Resistance [2022–2025] in 2022, respectively, aiming to promote the establishment of a fungal disease surveillance network and to improve the ability to standardize the diagnosis and treatment of IFD as well as the management of the clinical application of antifungal drugs in China (6,7). Meanwhile, the World Health Organization (WHO) issued the first global fungal priority pathogens list (FPPL) against IFD, which includes 19 pathogenic fungi. According to annual morbidity, drug resistance, mortality, complications and sequelae, IFD is divided into three priority levels: severe, high and moderate, with fungi common in China such as *Cryptococcus neoformans*, *Aspergillus fumigatus* and *Candida albicans* included in the serious priority level (8). The list clearly points out that improving public health interventions, regulating clinical diagnosis and treatment, increasing the monitoring of global fungal infections and pathogen resistance, and enhancing the development of diagnostic methods and therapeutic drugs are important strategies for IFD management. In addition, in the context of the novel coronavirus disease 2019 (COVID-19) pandemic, the incidence of COVID-19-associated invasive mycoses is about 12.6% and fungal diseases have become important complications, which further demonstrates the complexity and urgency of antifungal drug management (9-13). Currently, many countries have explored AFS programs and established relevant guidelines to improve the clinical

management, diagnosis and treatment of IFD, confirming that the use and promotion of AFS may improve the clinical treatment to a certain extent (14,15). However, due to significant differences in the IFD susceptible populations, incidence of various fungal diseases, drug resistance features and diagnostic and treatment protocols of different countries and regions, foreign AFS guidelines may not be fully applicable to China. Therefore, it is urgent to formulate an expert consensus for AFS-related basic metrics in line with our national conditions.

Objective

Based on the current understanding of AFS in China and the urgent need, led by the academicians Nanshan Zhong and Wanqing Liao, organized by the National Center for Respiratory Medicine of the First Affiliated Hospital of Guangzhou Medical University, the National Clinical Medical Research Center for Respiratory Diseases, and the Collaborative Group for Diagnosis and Treatment of Pulmonary Fungal Diseases; and considering consensus metrics of AFS in other countries, a list of metrics was developed based on China's national conditions and clinical experience of authoritative experts in various fields. Then authoritative experts in fields closely associated with IFD diagnosis and treatment were invited to investigate and discuss the proposed AFS metrics by applying the Delphi method. A consensus was finally reached, with the aim to provide a reference basis for standard clinical diagnosis and treatment, improve patient prognosis and control medical costs.

Methods

Members of the consensus development team

Under the leadership of the academicians Nanshan Zhong and Wanqing Liao (who did not participate in questionnaire filling), a total of 44 authoritative experts participated in questionnaire filling, including experts in respirology (n=24), hematology (n=7), intensive care medicine (n=2), microbiology (n=3), dermatology (n=3), infectiology (n=2) and pharmacology (n=3). In addition, one statistician was responsible for statistics-related work.

Metrics formulation

This consensus was based on the Basic Metrics for the Management of Antifungal Drugs in Hospitals published abroad in 2021: "Results of an international Delphi survey" (16), and a set of AFS metrics were preliminarily developed with reference to "the Guiding Principles for Clinical Application of Antibiotics (2015 edition)" (17) and "Evaluation indexes and requirements for clinical application management of antibiotics" (18) issued by the National Health and Development Commission, considering China's national conditions and the diagnosis and treatment experience of domestic authoritative experts. The retained metrics were classified into three aspects: right patient, right time and right use of antifungal drugs. Right use metrics were further subdivided into the drug choice, drug dosage, drug de-escalation, drug duration and drug consumption groups.

The Delphi process

This consensus applied the Delphi method. From September 2022 to February 2023, a preliminary AFS metric questionnaire was sent to the 44 members of the expert group by email for anonymous investigation (19). The background, purpose and methods of the establishment of this consensus were described in detail in the questionnaire, and experts were allowed to propose amendments and to include additional metrics in the comment column.

Statistical analysis

A five-level Likert scale was used to grade each metric (1, strongly agree; 2, agree; 3, neutral or uncertain; 4, disagree; 5, strongly disagree) (20). Results for each metric were measured by voting agreement rate, defined as the percentage of experts selecting "strongly agree" or "agree" (16). Currently, there is no recognized consensus ratio for the Delphi method, which generally ranges from 51% to 80% (21). This study considered an agreement rate of ≥80% as a consensus.

Results

Completion of the survey questionnaire by the expert group

This consensus issued a total of 44 questionnaires, and all 44 were well responded to, indicating a response rate of 100%. The expert group was generally highly motivated. The demographic characteristics of the experts participating in the questionnaire are shown in *Table 1*.

Table 1 Basic information of the experts who participated in the survey

Basic information	N (%)
Total number of experts	44 (100.0)
Main occupation	
Clinician and/or microbiologist	41 (93.2)
Pharmaceutical expert	3 (6.8)
Clinical area of expertise	
Respirology	24 (54.5)
Hematology	7 (15.9)
Intensive care medicine	2 (4.5)
Microbiology	3 (6.8)
Dermatology	3 (6.8)
Infectiology	2 (4.5)
Pharmacology	3 (6.8)
Years of experience in the field	
≤10 years	0
>10 years	44 (100.0)

Candidate metrics

This consensus initially proposed 43 metrics based on foreign AFS metrics (16) and the actual clinical situation in China. After investigation and discussion by the 44 experts, eight metrics were retained (metrics 3.1.1–3.1.3, 3.1.8, 3.2.3, 3.3.1, 3.5.1 and 3.5.2), three were modified (metrics 1.2, 3.1.5 and 3.2.4), and 13 were added. Finally, a total of 24 metrics were obtained (*Table 2*), including four for right patient, three for right time, and 17 for right use of antifungal drugs. Among these, agreement rates for 22 metrics were ≥80%, indicating a consensus.

Right patient metrics

Of the 24 metrics included in this study, four involved the "right patient" and all reached consensus, but a few experts had different opinions on some of them. For metric 1.1 "For patients with suspected IFD, imaging, etiology, serology [such as (1,3) β-d glucan test (G test), galactomannan test (GM test), candida antigen, cryptococcus capsular polysaccharide antigen, etc.] and histopathological examinations should be completed to confirm the etiological diagnosis. If conditions permit, it is recommended to use polymerase chain reaction (PCR), metagenomic next-generation sequencing (mNGS)/targeted next-generation sequencing (tNGS), nanopore sequencing and other tools to detect fungal nucleic acids to improve the diagnostic rate". For this metric, four experts (respirology, 2; dermatology, 1; hematology, 1) were cautious, because PCR and next-generation sequencing (NGS) and nanopore sequencing have not been standardized, PCR commercial detection kits are lacking, and NGS and nanopore sequencing were expensive with uncertain clinical value. According to metric 1.2 "When IFD patients receive empirical treatment, imaging, etiology, serology (such as G test, GM test, candida antigen, cryptococcus capsular polysaccharide antigen, etc.) examinations should be performed, combined with clinical response monitoring to comprehensively evaluate treatment efficacy, and the antifungal treatment plan should be adjusted accordingly", as the preliminary metrics in this investigation did not consider the evaluation of "treatment effect", one respirology expert selected "disagree". The latter expert suggested a comprehensive evaluation based on the patient's clinical response to empirical treatment, including evaluating the general condition of the patient, clinical symptoms (fever, dyspnea), whether the physical signs are improved, and the absorption of imaging lesions. Therefore, we improved the metrics accordingly. For metric 1.3 "Low-risk and medium-risk IFD patients with failed treatment with broad-spectrum antibiotics for 3–5 days showing persistent fever and other clinical symptoms, imaging, etiology, serology (such as G test, GM test, candida antigen, cryptococcus capsule polysaccharide antigen, etc.) and histopathological examinations should be performed as soon as possible. Meanwhile, low-risk and medium-risk IFD patients should undergo diagnosis and treatment". For this metric, one respirologist and one pharmacologist recommended not including low-risk patients, but did not explain the specific reasons, and two other respirologists suggested that low-risk patients should undergo a clear diagnosis before treatment initiation.

Right time metrics

There were three metrics concerning "right time" in this consensus. No consensus was reached on metric 2.1: "Prophylactic antifungal therapy can significantly benefit high-risk patients with IFD and is recommended for high-risk patients". A total of 10 experts (respirology, 6; infectiology, 2; pharmacology, 2) selected "remain neutral/uncertain", and the agreement rate was only 75.61%.

Table 2 AFS metrics included in the Delphi method-based questionnaire survey

Number	AFS metrics	Agreement rate (%)
1. Right patient (n=4)		
1.1	For patients with suspected IFD, imaging, etiology, serology (such as G test, GM test, candida antigen, cryptococcus capsular polysaccharide antigen, etc.) and histopathological examinations should be completed to confirm the etiological diagnosis. If conditions permit, it is recommended to use PCR, mNGS/tNGS, nanopore sequencing and other tools to detect fungal nucleic acids to improve the diagnostic rate	91.46
1.2	When IFD patients receive empirical treatment, imaging, etiology, serology (such as G test, GM test, candida antigen, cryptococcus capsular polysaccharide antigen, etc.) examinations should be performed, combined with clinical response monitoring to comprehensively evaluate treatment efficacy, and the antifungal treatment plan should be adjusted accordingly	92.68
1.3	Low-risk[a] and medium-risk[b] IFD patients with failed treatment with broad-spectrum antibiotics for 3–5 days showing persistent fever and other clinical symptoms, imaging, etiology, serology (such as G test, GM test, candida antigen, cryptococcus capsule polysaccharide antigen, etc.) and histopathological examinations should be performed as soon as possible. Meanwhile, low-risk and medium-risk IFD patients should undergo diagnosis and treatment[d]	92.68
1.4	Compared with empirical therapy, diagnostic-driven therapy based on imaging and laboratory findings can improve the accuracy of IFD diagnosis, reduce the irrational use of antifungal drugs, and save medical resources	91.46
2. Right time (n=3)		
2.1	Prophylactic antifungal therapy can significantly benefit high-risk patients with IFD[c] and is recommended for high-risk patients	75.61
2.2	There is no significant benefit from prophylactic antifungal therapy in low-risk patients with IFD, and prophylactic antifungal therapy is not recommended until definitive etiological evidence is obtained	90.24
2.3	Invasive mucormycosis is a rare fungal infection, and routine prophylactic antifungal therapy is not recommended	85.37
3. Right use (n=17)		
3.1 Drug choice (n=8)		
3.1.1	Antifungal therapy requires appropriate indications	97.56
3.1.2	The selection of antifungal drugs can refer to the antimicrobial spectra of the antifungal drugs	97.56
3.1.3	The selection of antifungal agents should follow evidence-based medicine guidelines	97.56
3.1.4	Breakthrough IFD[e] has poor prognosis, and well-tolerated, broad-spectrum, potent drugs are recommended for antifungal treatment	97.56
3.1.5	At the time of IFD treatment, the primary disease should be actively treated. To ensure the efficacy of antifungal therapy, antifungal drugs with less interactions with the drugs used to treat the primary disease should be selected	97.56
3.1.6	When multiple drugs are used concurrently, attention should be paid to the interactions of antifungal drugs with other drugs, and TDM should be performed if necessary	85.37
3.1.7	In case of intolerance to antifungal drugs or drug-related adverse reactions in IFD treatment, it is recommended to switch to antifungal drugs with enhanced safety and tolerance	100.00
3.1.8	According to the guidelines/consensus, restricted grade antifungals should be used only after discussion with the appropriate management team	87.80

Table 2 (*continued*)

Table 2 (*continued*)

Number	AFS metrics	Agreement rate (%)
3.2 Drug dosage (n=4)		
3.2.1	Prophylactic antifungal therapy with triazoles in high-risk IFD patients[c] should be performed with effective blood concentrations to ensure treatment effect, and TDM should be performed if necessary to avoid breakthrough IFD[e]	92.68
3.2.2	In IFD patients with liver and/or renal impairment, liver/renal function should be evaluated according to Child-Pugh grading criteria and/or endogenous creatinine clearance levels, and antifungal drugs and dosages should be reasonably selected on the basis of both efficacy and safety to avoid aggravating liver/renal function injury	97.56
3.2.3	According to the PK/PD characteristics of antifungal drugs, appropriate loading and maintenance doses are selected	100.00
3.2.4	If conditions permit, it is recommended to optimize the dosage of triazole antifungal drugs guided by TDM	100.00
3.3 Drug de-escalation (n=1)		
3.3.1	De-escalation from broad-spectrum to narrow-spectrum antifungal drugs based on drug susceptibility data and/or clinical treatment response and efficacy	92.68
3.4 Drug duration (n=2)		
3.4.1	According to IFD host immune status, infection pathogen site, type, drug susceptibility test, clinical type, disease severity and treatment response, individual treatment is given to ensure adequate treatment	97.56
3.4.2	In the course of IFD treatment, imaging, serology (such as G test, GM test, candida antigen, cryptococcus capsular polysaccharide antigen, etc.) and fungal drug resistance examinations should be performed regularly to comprehensively evaluate antifungal efficacy, determine disease outcome, and adjust the treatment duration appropriately	97.56
3.5 Drug consumption (n=2)		
3.5.1	DDD[f]	73.17
3.5.2	LOT[g]	87.80

[a], low-risk group for IFD: other lymphoproliferative tumors (e.g., standard chemotherapy for lymphoma, induction therapy for myeloma, primary treatment for chronic lymphocytic leukemia), other myeloproliferative tumors, or solid tumors undergoing treatment (22). [b], intermediate-risk group for IFD: autologous hematopoietic stem cell transplantation cases (e.g., patients at high risk for mucositis); allogeneic hematopoietic stem cell transplantation with expected neutropenia <14 days; lymphoma (e.g., receiving intensive or dose-escalation therapy) (22). [c], high-risk for IFD: neutrophils $<0.1\times10^9$/L lasting >3 weeks or $<0.5\times10^9$/L lasting >5 weeks (e.g., allogeneic hematopoietic stem cell transplantation); glucocorticoids >1 mg/kg equivalent of prednisolone and neutrophils $<1\times10^9$/L for >1 week; glucocorticoid >2 mg/kg prednisolone equivalent for >2 weeks; unrelated, mismatched, or cord blood allogeneic hematopoietic stem cell transplantation; widespread or severe graft-versus-host disease; acute myeloid leukemia undergoing induction or reinduction therapy; acute lymphoblastic leukemia undergoing induction or reinduction therapy; myelodysplastic syndrome (22); [d], diagnostic-driven therapy refers to patients with no clinical symptoms of infection or persistent neutrophil-deficiency related fever in response to broad-spectrum antimicrobial therapy. Combination of clinical imaging (e.g., imaging changes associated with aspergillus infection on chest CT) and microbiological markers (e.g., positive G test, positive GM test, positive fungal culture or microscopic examination of specimens obtained from non-sterile sites or non-sterile procedures) of IFD does not meet the antifungal therapy required for the diagnosis or clinical diagnosis of IFD; [e], definition of breakthrough IFD: any IFD occurring during antifungal exposure, including fungi not covered by the antifungal spectrum, in patients administered prophylactic therapy, empire-based therapy, diagnostic-driven therapy, and target therapy (23). [f], DDD, i.e., average daily dose of a particular drug used to treat the main indication in adults, as determined by the WHO Collaborating Centre for Pharmaceutical Statistical Methods based on the recommended dose of drugs commonly used in different countries, and constantly revised by an international panel of experts (24,25); [g], LOT, which refers to the duration of antifungal therapy, can be expressed as the median number of treatment days or the average treatment duration for a specific indication (26). AFS, antifungal stewardship; IFD, invasive fungal disease; G, (1,3) β-d glucan; GM, galactomannan; PCR, polymerase chain reaction; mNGS, metagenomic next-generation sequencing; tNGS, targeted next-generation sequencing; TDM, therapeutic drug monitoring; PK/PD, pharmacokinetics/pharmacodynamics; DDD, defined daily dose; LOT, length of therapy; CT, computed tomography; WHO, World Health Organization.

The members of the expert group believed that the definition of high-risk patients with IFD in the preliminary metric questionnaire was not clear enough, and that the initiation of prophylactic antifungal therapy should not be determined solely by a single risk factor, but also consider the patient's immune status, clinical manifestations, imaging and serological results, infection site, and disease severity. Additionally, attention should be paid to the harmful effects of structural lung diseases and severe viral pneumonia in patients with IFD, emphasizing the clinical values of preventive and preemptive antifungal treatments for such patients. As for the initial research metric 2.3 "Invasive mucormycosis (IM) is a rare fungal infection, and routine prophylactic antifungal therapy is not recommended", two respirology experts suggested increasing evidence indicates that IM is not a rare fungal disease, especially in patients with hematological malignancies. Additionally, due to the rapid progression of IM and its high mortality, one dermatology expert recommended that the etiological diagnosis should be actively clarified and, if necessary, broad-spectrum antifungal drugs should be used for preventive treatment in case of relatively clear risk factors. At present, the metric has been modified and supplemented according to expert opinions.

Right drug metrics

Drug choice

Among the 17 metrics of "right use", 8 involved "drug choice" and all reached a consensus. Of these, the agreement rate for 3.1.7 "In case of intolerance to antifungal drugs or drug-related adverse reactions in IFD treatment, it is recommended to switch to antifungal drugs with enhanced safety and tolerance" was 100%.

As for metric 3.1.4 "Breakthrough IFD has poor prognosis, and well-tolerated, broad-spectrum, potent drugs are recommended for antifungal treatment", one pharmacology expert selected "disagree", arguing that targeted treatment should be carried out after identifying the pathogenic organisms. Another three experts (respirology, 1; infectiology, 1; pharmacology, 1) put forward relevant suggestions to improve the metric: according to the changes of clinical diseases, the detection of pathogenic microorganisms and the clear cause of breakthrough, a comprehensive selection of better-tolerated, broad-spectrum and powerful antifungal drugs should take into account the safety and efficacy of drugs.

As for the metric 3.1.5 "At the time of IFD treatment, the primary disease should be actively treated. To ensure the efficacy of antifungal therapy, antifungal drugs with less interactions with the drugs used to treat the primary disease should be selected", one infectiology expert selected "remain neutral/uncertain" and suggested specific analysis according to patient condition and fungal type. Meanwhile, one pharmacology expert suggested adding the prerequisite of "under the condition of equal efficacy". At present, the metrics has been modified and supplemented according to expert opinions.

Drug dosage

Consensus was reached on four "drug dosage" metrics, of which "According to the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of antifungal drugs, appropriate loading and maintenance doses are selected" and "If conditions permit, it is recommended to optimize the dosage of triazole antifungal drugs guided by therapeutic drug monitoring (TDM)" had 100% agreement.

Regarding the metric "Prophylactic antifungal therapy with triazoles in high-risk IFD patients should be performed with effective blood concentrations to ensure treatment effect, and TDM should be performed if necessary to avoid breakthrough IFD", two respirology experts selected "remain neutral/uncertain" and one pharmacology expert selected "disagree", for the following reasons: it is necessary to emphasize the application and evaluation of fungal pathogen detection and related laboratory metrics, to strictly control the indications of empirical or preventive treatment, and to avoid drug abuse; prophylactic drugs are not equal to therapeutic drugs, and the related duration and dosage are difficult to control clinically. In addition, the selection of prophylactic drugs for different underlying diseases is also different, e.g., fluconazole is not recommended for patients with high risk of invasive aspergillosis (IA).

Drug de-escalation

This consensus only involved one metric of "drug de-escalation", that is, "De-escalation from broad-spectrum to narrow-spectrum antifungal drugs based on drug susceptibility data and/or clinical treatment response and efficacy". The agreement rate for this metric exceeded 90%. The four experts (respirology, 2; dermatology, 1; pharmacology, 1) who selected "neutral/uncertain" or "disagree" believed that drug sensitivity results are not necessarily consistent with the treatment effect; if the existing scheme is effective, it cannot be replaced or adjusted.

Drug duration

There were two metrics related to "drug duration", with agreement rates above 90%. For the metric "In the course of IFD treatment, imaging, serology (such as G test, GM test, candida antigen, cryptococcus capsular polysaccharide antigen, etc.) and fungal drug resistance examinations should be performed regularly to comprehensively evaluate antifungal efficacy, determine disease outcome, and adjust the treatment duration appropriately", one respirology expert suggested that the improvement of clinical symptoms should be evaluated at the same time, and in determining disease outcome, attention should be paid to distinguishing between recurrence and reinfection.

Drug consumption

There were two metrics related to drug consumption. Of these, "defined daily dose (DDD) adjusted according to bed usage" had an agreement rate of only 73.17%. The reasons for the disagreement were as follows: fungal infections are complex, and IFD incidence varies in hospitals at different levels in different regions. In addition, IFD antifungal therapy should determine the drug duration according to the patient's condition and individual situation, to ensure adequate, sufficient and individualized treatment; therefore, it is unreasonable to evaluate the drug duration by the DDD alone. Although a consensus was reached on the metric "length of therapy (LOT)", three respirology experts still selected "neutral/uncertain" and two experts (respirology, 1; pharmacology, 1) selected "disagree" or "strongly disagree" because of differences in the individual immune status of patients, the type of fungal infection and clinical classification. There is a significant difference in the duration of antifungal treatment (for example, cryptococcal infection of the artificial heart valve requires lifelong treatment), so individualized treatments should be followed; in addition, the drug duration of antifungal drugs is mostly long, and the evaluation metric LOT is not appropriate as the duration of AFS.

Discussion

The consensus development team consists of experts from different fields, most of whom are respiratory experts, because in China respiratory experts are mainly responsible for treating pulmonary infectious diseases, while infectious disease specialists are mainly responsible for treating liver diseases and tuberculosis.

In recent years, many studies have shown that standardized implementation of AFS significantly improves the diagnosis and treatment of IFD, improves patient prognosis and reduces medical costs (27-29). The selection of appropriate patients for suitable antifungal therapy (such as prophylactic, diagnostic-driven, empirical, or targeted therapy) is an important prerequisite for standardized implementation of AFS. Multiple studies have confirmed that interventions based on AFS metrics significantly increase not only the rate of patients switching from empirical or fever-driven therapy to imaging, microbiology, and serology-based diagnostic-driven treatment, but also the rate of patients administered antifungal management based on a diagnosis (27,30,31). Compared with empirical therapy, diagnostic-driven therapy significantly reduces clinical treatment costs while selecting the right patients without affecting overall survival (32,33). All four "right patient" metrics in this consensus were agreed upon. Most experts suggested that in patients with suspected IFD, imaging, etiology, serology (such as G test, GM test, candida antigen, cryptococcus capsular polysaccharide antigen, etc.) and histopathological examinations should be performed as soon as possible to confirm the etiological diagnosis. If conditions permit, it is recommended to use PCR, mNGS/tNGS, nanopore sequencing and other tools to detect fungal nucleic acids to improve the diagnostic rate (34,35).

With the increasing proportion and diversity of immunosuppressed hosts, another key approach to AFS is to emphasize the importance of initiating antifungal therapy at the right time to improve patient outcomes. In this consensus, there were three metrics associated with the "right time of antifungal therapy", but no agreement was reached on "Prophylactic antifungal therapy can significantly benefit high-risk patients with IFD and is recommended for high-risk patients". A Chinese multicenter study divided patients with hematological malignancies administered chemotherapy into the high- (risk score >15), medium- (risk score 11–15) and low- (risk score 0–10) risk groups according to the independent risk factors for IFD, and found that the high- and medium-risk groups benefited from preventive antifungal therapy. The incidence rates of IFD decreased from 23.3% and 6.6% to 8.4% and 2.1% (P=0.007) in the high- and medium-risk groups, respectively, while the incidence of IFD in low-risk patients did not decrease and even increased from 0.6% to 2% (P=0.004) (36). Although current Chinese and international guidelines recommend prophylactic antifungal therapy for individuals at high risk of IA [such as individuals with allogeneic hematopoietic stem cell

transplantation (Allo-HSCT) with prolonged neutropenia, extensive or severe graft-versus-host disease (GVHD), acute myeloid leukemia (AML) receiving intensive induction or reinduction therapy, etc.] (32,37,38), 24.39% of experts in the current consensus were "neutral/uncertain" about this view, due to differences in the definitions of high-risk patients with IFD in different guidelines and because no one risk factor alone can determine whether to initiate prophylactic antifungal therapy. The patient's immune status, clinical manifestations, imaging and serological findings, infection site and disease severity should be considered to make a comprehensive judgment. Compared with IA, IM is relatively rarer in clinic, and no evidence-based medical data support IM prevention. Therefore, this consensus does not recommend routine preventive treatment for Mucor infections.

The third important component of this consensus is the right use of antifungals, including drug choice, therapeutic dosage, treatment duration, timing of step-down from broad-spectrum to narrow-spectrum drugs, drug consumption, etc. This consensus suggests that the selection of antifungal drugs should take into account the patient's primary disease, liver and kidney functions and complications, and after comprehensive consideration of indications, contraindications, antifungal spectrum, strain resistance, tolerance, drug interactions, clinical efficacy, drug dosage adjustment principle and other aspects of antifungal drugs, to ensure that under the condition of equal efficacy, antifungal drugs with less drug interactions and better safety are selected (39-45).

Any IFD occurring during antifungal exposure, including a pathogenic fungal infection not covered by the antifungal spectrum of the drug, is termed a breakthrough IFD. There are many risk factors for breakthrough IFD, mostly including the host, fungal and iatrogenic aspects, e.g., host use of immunosuppressants, resistance to antifungal drugs, inappropriate selection of antifungals or substandard blood concentrations. It is worth noting that the absorption, distribution, metabolism, and clearance of antifungals are easily affected by multiple factors such as host immune status, underlying diseases, co-administration of drugs, infection by inherently resistant fungi or acquired infections during treatment, and antifungal resistance (46), while breakthrough IFD generally has a poor prognosis. Therefore, this consensus recommends the selection of well-tolerated, broad-spectrum and potent antifungal drugs for treatment.

TDM is an important tool to ensure efficacy, effectively avoiding excessive drug exposure, reducing drug-related adverse reactions, and avoiding treatment failure due to underdose, and optimizes the management of IFD, especially for specific antifungal drugs with significant exposure-response relationships and unpredictable PK/PD characteristics or narrow drug treatment indices (47). Therefore, this consensus recommends that when a triazole drug is used in IFD patients, TDM should be used to optimize the drug dosage according to the guideline recommendation, to ensure the drug quickly reaches the target blood concentration, to ensure its efficacy and to reduce adverse reactions, ultimately achieving the purpose of optimizing clinical efficacy and minimizing toxicity (31,48,49).

At present, LOT is mostly used to evaluate the duration of antibiotic treatment, and has not been comprehensively evaluated in combination with the doses of the drugs used. Although a consensus was reached on LOT as a metric of drug consumption, due to the complexity of fungal infections, there are differences in the incidence rates of diseases and IFD in hospitals at various levels. In addition, there are significant differences in the duration of antifungal therapy for individuals with different immune backgrounds and treatment duration for different types of fungal infections. Therefore, IFD antifungal therapy should follow the principle of individualization, and LOT should not be used as the sole evaluation metric of AFS consumption. The DDD is one of the commonly used AFS metrics, which refers to the average daily dose of a given drug employed to treat the main indications in adults (50,51). Because DDD values can be obtained directly from pharmacy dispensing records, this metric has certain advantages in health care facilities relying on paper records. Therefore, most current studies have only used the DDD to record, monitor, compare, or evaluate the use of antifungal drugs across healthcare facilities (24,31,39,40,48,49,52-57). However, due to the long-term treatment of IFD patients, it is difficult to obtain complete out-of-hospital treatment records, and treatment duration cannot be accurately assessed. Therefore, the disadvantages of using the DDD as a metric of AFS are also obvious. In addition, the treatment of fungal infections is complex, and the duration of antifungal treatment must be determined according to the patient's condition. Furthermore, there are obvious differences in the types and incidence rates of IFD in hospitals at various levels, and DDD values differ by region or ethnicity. Consequently, there are obvious limitations in using the DDD as a metric of therapeutic expenditure for AFS.

Conclusions

In summary, this consensus provides a comprehensive literature review on AFS metrics, adopting the Delphi method for anonymous voting to avoid the mutual influence of experts (58). This consensus establishes AFS standards in China and is the first AFS consensus in Asia. The strength of this consensus is that the interviewed experts were widely representative and authoritative, covering respirology, hematology, intensive care medicine, infectiology, pharmacology, microbiology, dermatology and statistician. The metrics investigated fully consider the actual clinical situation in China, involving right patients, right time, and right use of antifungal drugs. Most metrics (22/24, 91.7%) reached consensus. The proposal of these metrics may provide a reference basis for the management and monitoring of IFD in medical and healthcare institutions, improve the standard of clinical diagnosis and treatment of IFD, promote the rational use of antifungal drugs and improve patient prognosis.

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Footnote

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