A Practical Guide to Implementing and Improving Antifungal Stewardship

ASIA FUNGAL WORKING GROUP
an ISHAM working group

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A Practical Guide to Implementing and Improving Antifungal Stewardship Programs in Asian Hospitals

This document is intended to provide a practical step-by-step guide for the implementation and/or improvement of antifungal stewardship (AFS) programs in Asian hospitals in a cost-containing manner. The information contained in the guide is consistent with recommendations from internationally recognized organizations, while taking into account the uniqueness and challenges of managing invasive fungal disease (IFD) in these regions. The document provides core recommendations based on the Mycoses Study Group Education and Research Consortium (MSGERC) in association with the Infectious Diseases Society of America (IDSA).[1] Expert recommendations or counter-measures for challenges specific to Asia are then provided to facilitate implementing or optimizing AFS in a real-world setting. Additional AFS resources are summarized with links in **Appendix 1** and two case studies of AFS interventions used in Asia are also provided in **Appendix 2**.

Core elements of an AFS program

The implementation of AFS program strategies will depend on the needs and resources of individual hospitals, but there are seven key elements outlined in this guide (**Figure 1**) that will ensure your program aligns with evidence-based international best-practice guidance to encourage appropriate use of antifungal agents, minimize fungal resistance selection pressures, improve multidisciplinary communication and optimize patient outcomes while increasing cost-effectiveness.[1,2]

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Figure 1

Core program components for antifungal stewardship[1]

1. **Engagement of senior leadership**
   Engage senior hospital leaders which includes accountability and dedicated resources to support AFS activities
2. **Accountability & responsibilities**
   Gather a highly functioning, experienced, multidisciplinary AFS team that includes ID physicians, ID-trained pharmacists and other key healthcare personnel managing these diseases
3. **Expertise in infection management**
   Set up timely access to conventional and non-culture-based diagnostic testing for *Candida* and *Aspergillus* species
4. **Education & training**
   Develop education and practical training through targeted programs to address knowledge gaps

5. **Promote responsible antifungal use**
   Initiate actions aimed at responsible antimicrobial use, such as ID consultation for patients with IFI and development of treatment bundles or guidelines
6. **Monitoring & surveillance**
   Monitoring, surveillance and reporting of fungal infections with access to timely antifungal susceptibility testing
7. **Reporting & feedback**
   Reporting and feedback mechanisms to track antifungal drug use

Key steps towards implementing the core components of AFS programs

Step 1: Engagement of senior hospital management leadership

MSGERC recommendation:[1]

AMS and AFS goals should be integrated into hospital strategic plans and policies with senior leadership engagement, accountability, and dedicated resources to support these activities.

One of the critical first steps towards implementing an AFS program is to gain the support of senior hospital leadership, without which it will be difficult to nurture stewardship goals.[1] Advocacy at the executive level is necessary to ensure that AFS is included in budgets, strategic plans, performance improvement priorities, job descriptions and an institution's annual targets.[1]

Challenges specific to Asia:

The main challenge in Asia is the relatively low awareness of the importance and seriousness of IFD across all levels of hospital hierarchy.[3] From hospital administrators and funding agencies through to clinicians and microbiologists, fungal pathogens are mostly ignored, despite posing a significant threat to public health.[3,4] **According to one survey of Asian clinicians, only 30% had an AFS program at their hospital.**[3] Another difficulty is that population-based surveillance – of the incidence/prevalence of IFD and of the geographic distribution of antifungal-resistant isolates – is lacking in low- and middle-income countries (LMICs).[5-7] Without published local data to demonstrate the incidence and burden of fungal infections and resistance patterns to available drugs, the importance of IFD will remain under-recognized.[4-6]

Expert recommendations for resource-limited settings:

- **Raise awareness** of the severity of IFDs and convince hospital authorities that AFS activities are essential in facilities where antifungals are used.[1,8]
  - Administrators are frequently faced with the challenge of prioritizing the

funding of multiple competing programs.[1] ***Collect data*** to demonstrate cost savings and morbidity/mortality impact after the implementation of AFS (to ensure continuous support from leadership).[1]

- **Identify leaders** who can champion AFS.[1]
- **Associate with existing AMS programs** in the hospital, if appropriate.[1,7] Ideally, an AFS program should be separately implemented due to several distinctive features. However, where a resource-constrained environment limits provision of a separate program, AFS may be incorporated into existing AMS programs as long as care is taken to ensure that AFS components are not overwhelmed and overtaken by antibacterial stewardship.
- **Advocacy** showing examples from other hospitals in similar limiting settings.[1]
- **Foster collaboration** between the AFS team and various hospital committees.[8]
- **Promote accreditation** of the hospital and include AFS in accreditation.[8]

Step 2: Accountability and responsibilities

MSGERC recommendation:[1]

1. Core members of an AFS team should have in-depth **knowledge** and clinical **experience** in the management of IFD in pertinent patient populations, including fungal epidemiology and susceptibility patterns; laboratory diagnosis of IFD; spectrum and pharmacokinetics of antifungal drugs; strategies for optimizing antifungal dosing and duration; fungal surveillance; and anticipating, interpreting, and managing drug–drug interactions, antifungal toxicities, and their management, as well as interpretation of therapeutic drug monitoring. This would include, whenever possible, infectious diseases (ID) physician(s) and ID-trained pharmacist(s).
2. We recommend that AFS teams develop ongoing collaborative strategies to engage key practitioners who most frequently manage IFD (eg, weekly clinical rounds), or include clinical specialists from high-prescribing specialties as core team members in stewardship discussions involving antifungal therapies.

The management of IFD is a complex and challenging task which warrants the involvement of qualified experienced members to guide and facilitate the timely initiation and optimal selection of antifungal agents at appropriate doses across various patient settings.[1,2] The establishment of a highly functioning multidisciplinary AFS team is therefore crucial to the success of this type of program.[1,2]

Challenges specific to Asia:

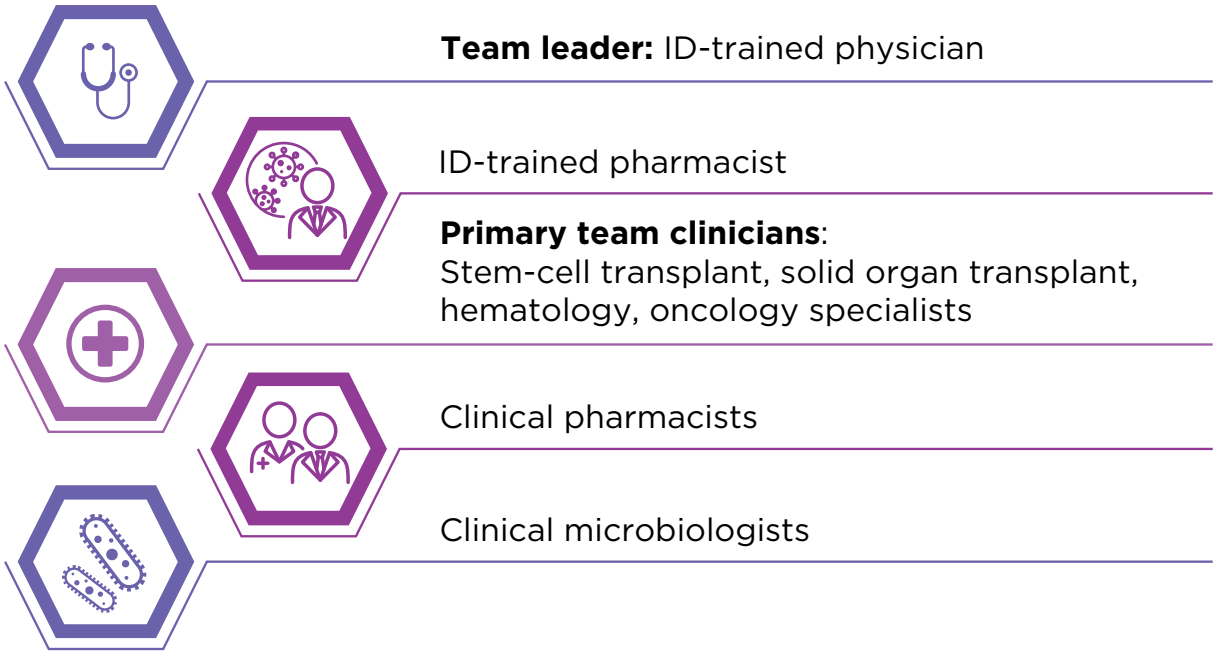
Building an AFS team may be hindered by generalized low awareness of IFD as well as a lack of training, meaning limited availability of expertise and manpower.[3,6,9] Fungal infections occur across a range of patient populations and may be handled by different specialists.[6] **Some clinicians in Asia only handle 2-4 proven cases monthly,** most use empiric therapy,[3,6] and IFD can mimic tuberculosis which can lead to over- or under-treatment with empiric therapy.[7] Moreover, ID specialists are rare in Asian countries[10,11] and formal training in medical mycology is often lacking, with 45% of ID specialists stating they have not received any.[3,6]

Expert recommendations for resource-limited settings:

- Develop an AFS team with defined responsibilities and identify a 'creditable local expert' who can provide the lead and conduct training for others.[7,8]
  - **Appoint, if possible, or train up an AFS lead** who has in-depth knowledge and clinical experience across all components

Figure 2

Suggested core members of an AFS team[12]



of IFD management to be responsible for oversight and outcomes reporting (e.g. ID physician, ID-trained PharmD or other specialist familiar with antifungals).[1,2,10]

- **Appoint other key team members** (see **Figure 2**). This may include key clinicians who use antifungals as critical components of treatment protocols for other specialties.[1] ID-trained clinical pharmacists and microbiologists are also recommended as key members.[1,2]

- **Engage in educational programs and training.**[7,8]
  - Provide targeted training in AFS principles to any person who is likely to prescribe antifungals.[1]
- **Develop telehealth support** to access outside ID expertise where the needed expertise is not available.[1,8]
- **Develop local guidelines** based on local epidemiology and follow them[7] (see also Step 5).
- **Increase the number of ID physicians/ pharmacists** who can devote time to AFS.[10]

Step 3: Expertise in infection management

MSGERC recommendation:[1]

We recommend that centers that frequently manage patients with IFD have access to **timely** conventional and non-culture-based **diagnostic testing** for *Candida* and *Aspergillus* species.

Diagnostic stewardship is an important component of any AFS program.[1] **Having expertise in fungal diagnostics is necessary for fungal identification and because early and accurate diagnosis of IFD strongly influences appropriate prescribing and patient outcomes.**[1,13] The conventional cornerstone of fungal diagnostics is direct microscopy, histopathology and culture, but difficulties arise from relatively low sensitivity, slow turnaround time, laborious processes and the need to obtain specimens via invasive means.[14] The introduction of non-culture-based rapid diagnostic tests (both serological and molecular) seeks to overcome some of these obstacles (**Table 1**).[1,14] Serological testing allows detection of antigens or antibodies in serum

Table 1

Key tests to improve diagnosis of invasive candidiasis and invasive aspergillosis[1,7,13,15]

Candidiasis	Aspergillosis
Gold standard: blood culture (sensitivity 50%) MALDI-TOF spectrometry for species identification Multiplex PCR (1,3)-ß-D-glucan assay for identifying deep-seated infection (or exclusion of candidiasis) T2 magnetic resonance	*Gold standard*: direct visualization of branching septate hyphae in tissue or recovery of *Aspergillus* from a sterile site Galactomannan antigen detection: ELISA, lateral flow assay, or lateral flow device Lateral flow assay and lateral flow device (1,3)-ß-D-glucan PCR High-resolution CT of the chest CT pulmonary angiography (optimal)

CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; PCR, polymerase chain reaction

or other body fluids when fungal infection is suspected. Molecular tests require further standardization before using them routinely.[14]

Challenges specific to Asia:

The main challenges with respect to implementing diagnostic recommendations are:

- **Lack of lab space, manpower or dedicated equipment necessary for fungal testing.**[9]
- **Inadequate access to rapid serological and/or molecular fungal detection tests.** Most Asian hospitals (~98%) have access to microscopy and histopathology, but the ability to obtain newer, more rapid tests (eg galactomannan, ß-D-glucan, various biomarker and PCR tests) is variable and ranges anywhere from 8% to 88% depending on which test is being considered.[3,9,16,17]
- **Inability to access tests in a timely manner.**[10,17] Some hospitals only have access to tests during standard weekday working hours[10] and 63% of labs performing 'rapid' galactomannan antigen detection only perform it 1-2 times per week.[17] This is a long turn-around time that could have serious implications for patients with life-threatening aspergillosis.[17]

Expert recommendations for resource-limited settings:

- **Integrate available resources** where possible (eg, perform non-culture-based diagnosis in a central lab facility that can be accessed by multiple hospitals) to reduce costs in resource-limited settings.[1]
- Promote access to **timely conventional and non-culture-based diagnostic testing**[1] and advocate for:
  - **WHO essential diagnostic tests** (microscopy, histopathology, culture, *Aspergillus* antigen & antibody, etc.).[8,19]
  - **WHO verified point-of-care tests** (lateral flow assays for *Aspergillus* galactomannan, *Aspergillus*-specific IgG and IgM antibodies).[7,20]
- When no diagnostic test is available, **use clinical predictive rules** to identify ICU patients not developing invasive candidiasis.[21,22]
- **Simplify the diagnostic criteria**, as in other LMICs for chronic pulmonary aspergillosis.[7,18]

Step 4: Education and training

MSGERC recommendation:[1]

We recommend the development of targeted educational programs as part of a multifaceted AFS program to address knowledge gaps in the interpretation of microbiology laboratory results, differentiation of colonization vs infection, indications for prophylaxis vs empiric therapy, and antifungal therapy dosing and monitoring.

Numerous studies worldwide have shown that gaps in prescriber's knowledge are frequent when it comes to AFS (see box above).[1] Targeted education programs to address these gaps can be effective, but may be short-lived and therefore require regular repetition.[2]

Challenges specific to Asia:

There is a need to improve the quality of mycological education for both undergraduates and post-graduates in many Asian countries.[3,7] **In one survey of several Asian countries, 63% of respondents had received no specific training on fungal infections.**[3] More than half (53%) stated that their medical school mycology training as poor and over a third (35%) rated their subsequent post-graduate training as poor.[3] The same survey also found that a majority of non-ID physicians (84%) failed to use the services of an ID colleague when managing IFD in their patients.[3]

Expert recommendations for resource-limited settings:

- **Prepare and distribute pocket cards** with recommendations about choice of antifungal, dosage, duration and drug interactions, based on local guidelines.[8,23]
- **Raise awareness of, and make available, free online resources** for education and training[7,8] (see Appendix 1).
- **Implement an AFS training program tailored** for your institution or local needs.[8,24]
- **Advocate for** the incorporation of medical mycology education into the medical graduate and postgraduate curricula.[6]
- **Implement a 'train the trainers' program** and develop a network of expert clinicians.[8]
  - Provide opportunity for regular interactions between a broad range of specialists (ie, microbiologists, emergency physicians, pulmonologists, transplant physicians, HIV physicians, hematologists, oncologists, intensivists, otorhinolaryngologists, neurologists, endocrinologists, nephrologists, internists, ophthalmologists, surgeons and dentists).[6]
  - Institute workshops to improve bedside practice through case-sharing of clinical presentations and diagnostic and therapeutic stewardship.[6]
  - Train at least frontline physicians to recognize diagnostic 'red flag' signs and symptoms in key patient populations for important IFDs and to know when to ask for an ID consult.[6]
  - Encourage participation in online educational programs driven by national or international societies.[7]
  - Members of the AFS team should regularly discuss, consult and share experience among themselves.[1]
- **Re-certify prescribers** for up-to-date AFS training.[7]

Step 5: Promote responsible antifungal use

MSGERC recommendation:[1]

1. We recommend, whenever possible, that **ID consultation** be performed for patients with IFDs such as fungemia, invasive aspergillosis, mucormycosis, and cryptococcal meningitis.
2. We recommend the development of **institutional care pathways** or **treatment bundles** as well as **guidelines** to improve the probability that diagnostic and therapeutic interventions for IFD are delivered in a timely and logical sequence to maximize patient outcomes and provider education.
3. Ongoing interventions such as **"handshake stewardship rounds"** or **post-prescription review and feedback** should be considered an essential part of a comprehensive AFS approach.
4. We recommend that facilities **evaluate the quality of antifungal prescribing** on a systematic basis, and use data-driven strategies to further optimize AFS interventions.

The mortality rate associated with IFD is among the highest of all infectious disease, partly because many of those who acquire fungal infections are critically ill or immunocompromised.[1] Moreover, the majority of antifungals are fungistatic.[43] This makes it important to develop and use locally-appropriate guidelines and management protocols to direct the responsible prophylactic, empiric and therapeutic use of antifungal agents.[1,2] Guidelines are more likely to be accepted and used if they are adapted to local circumstances with input from senior clinicians who are experienced with antifungal use.[2]

Challenges specific to Asia:

Few, if any, local or national guidelines exist in the Asian region and many ID specialists resort to using IFD guidelines from IDSA or the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).[3] On the other hand, non-ID specialists are less likely to follow international guidelines and prefer to use institutional guides, probably reflecting a knowledge gap that leads them to resort to their hospital's website or intra-departmental guide for help.[3] This creates an opportunity for the uptake of locally-produced guidelines and care bundles. Drug choices are also more limited in Asia with affordability and availability being the most common reasons for not using a particular drug (80% and 34%, respectively).[3,6,16,25] Added to this is a lack of health information and clinical decision support systems to help improve antifungal use and evaluate the success of AFS strategies (see Step 7).[5,8,26,27]

Expert recommendations for resource-limited settings:

- **Develop local guidelines** and raise awareness of appropriate national and/or international guidelines among key prescribing groups.[1,28]
  - Make them available at the point-of-care (eg, embedded within clinical decision support systems or readily accessible on the hospital intranet) and integrate them into daily workflow.[1,2]
  - Simplify their complexity by creating short, easy-to-follow summaries for quick-reference (ie, '**clinical care pathways**' or '**treatment bundles**'; see Figure 3).[1,2] Start with care bundle examples from international guidelines and modify them to comply with local scenarios and make them practical and easy to follow.[1,2]
- **Optimize the use of accessible and affordable antifungals**.[3,7,13]
  - Allow the use of azoles rather than

echinocandins when patients cannot afford azoles (except for *Candida auris* because the South Asian clade is universally resistant to fluconazole).
  - Clinicians should know how to infuse amphotericin B deoxycholate when lipid preparations are not available or affordable.
- **Implement 'handshake stewardship rounds' or post-prescription review and feedback.**
  - This focuses on 'face-to-face' interactions and the building of collegial relationships to enhance AFS uptake.[29]
- **Consider pre-authorization approaches.**
  - Pre-authorization may be a good option when education levels are low, but it requires an internal formulary and may be challenging to implement when timely review is necessary for optimal antifungal outcomes.[1,8]

Figure 3

Example: Clinical care bundles for invasive candidiasis and aspergillosis[1]

Invasive candidiasis management bundle	Invasive aspergillosis management bundle
At therapy initiation • Perform 2 high-volume blood cultures (40ml) prior to starting therapy • Removal of existing CVCs within 24h of diagnosis • Initial appropriate selection and dosing of antifungals considering local epidemiology started within 12h of culture • Ophthalmological exam within the first week of diagnosis	**At therapy initiation** • Serum GM test repeated twice in patients not on mold-active azole prophylaxis • CT imaging of chest and/or sinus/brain in patients with symptoms localized at these signs • Early bronchoscopy (within 48h) with cytology examination and culture of BAL fluid, measurement of GM antigen titer in BAL; transbronchial biopsy if feasible • Initial appropriate selection and dosing of antifungal agents considering previous antifungal exposure and local epidemiology • Systematic screening for drug interactions for any patient starting or stopping a triazole antifungal agent
After starting therapy • Follow-up blood cultures daily until clearance of candidemia is documented • Echocardiography in patients with persistent fungemia, fever, or new cardiac symptoms • Assessment of clinical efficacy 3–5 days after starting therapy and evaluating the need for alternative therapy based on when culture identification and susceptibility results are available • Administration of at least 2 weeks of therapy after clearance of blood cultures (longer with organ involvement) • Step-down to oral fluconazole therapy in patients with a favorable clinical course and an isolate with documented susceptibility	**After starting therapy** • Periodic (eg, weekly) testing of serum GM (if aspergillosis) as an adjunct criterion to assess treatment response • TDM of voriconazole and posaconazole and possibly isavuconazole serum levels to document adequate drug exposures • Assessment of therapy appropriateness based on microbiological, culture, or histological results • Repeat chest CT imaging after 3–4 weeks and periodically based on response, to assess infection status and/or progression • Step-down to oral triazole therapy in patients with a favorable clinical course

BAL, bronchoalveolar lavage; CT, computed tomography; CVC, central venous catheter; GM, galactomannan; TDM, therapeutic drug monitoring.

Adapted from: Johnson MD, et al. 2020.

Step 6: Monitoring and surveillance

MSGERC recommendation:[1]

1. We recommend that all centers that manage patients with IFD establish or adapt local surveillance systems for fungal infections to support AFS program initiatives.
2. We recommend that centers routinely managing IFD have access to timely antifungal susceptibility testing.
3. We recommend that centers that perform routine antifungal susceptibility testing develop cumulative antifungal susceptibility reports.
4. We recommend that AFS promote rational diagnostic testing and that the results of both fungal culture and non-culture-based tests are communicated to AFS teams to facilitate "real-time" interventions.
5. We recommend that all patients have their medication record screened by a clinical pharmacist or clinician to carefully assess for antifungal drug interactions. This should also be performed when starting and stopping concomitant medications.
6. We recommend that centers routinely managing patients IFD have access to timely TDM for triazole antifungal agents.

It is necessary to have adequate local surveillance systems in place to be able to continually monitor and address fluctuating epidemiology patterns, assess IFD burden, detect threats from newly emerging drug resistance and provide ongoing AFS effectiveness assessments.[1] The screening of medication records by an AFS team member is recommended based on the high likelihood of polypharmacy and the potential for drug-drug interactions among the critically ill patients commonly requiring antifungals.[1] Therapeutic drug monitoring (TDM) is recommended because triazole antifungals are subject to pharmacokinetic variability and TDM can reduce the risk of treatment failure or toxicity due to altered pharmacokinetics.[1,2]

Challenges specific to Asia:

Population-based surveillance of isolates resistant to antifungal agents is generally lacking in Asia.[5] Available data are fragmented and not representative, thereby preventing health policy makers from determining efficient allocation of funding and financial resources to programs that mitigate resistance.[5] **Although routine use of susceptibility testing can help guard against growing resistance levels, up to 41% of regional labs do not conduct such tests, and of those that do, only 38% use the standard microbroth dilution technique.**[17] Many labs perform susceptibility tests on yeasts, but only 27% perform tests on mycelial fungi.[17] Lack of access to newer methods (MALDI-TOF and sequencing) means many labs would fail to identify multidrug-resistant *C. auris,* one of the key pathogens now listed on the WHO Fungal Priority Pathogens list.[17,30,31]

In terms of patient monitoring once antifungal therapy has been initiated, over 80% of physicians use clinical parameters and 74% use imaging and blood cultures, but only a third use galactomannan.[3] The use of TDM during azole therapy is minimal in Asia.[3,17] Use by labs range from <10% to ~25%, and even when it is used, access can vary depending on which antifungal agent is being monitored.[3,16,17]

Expert recommendations for resource-limited settings:

- **Implement or improve infection control procedures**.[32] This will minimize the number of infections to be handled in the hospital.[33] (For more detail, see AMS Blueprint Guide to Infection Control)

- **Identify and define patient populations for TDM**.[1,2]
  - If possible, implement TDM for patient populations who are likely to have unpredictable oral drug absorption if receiving oral azoles (eg, those with diarrhea, vomiting, altered organ function, or who are pediatric, obese, or critically ill).
  - ***Where TDM is not available***, perform the following progressive steps: check compliance, stop interacting drugs (if possible), use more bio-available formulations (eg, posaconazole tablet instead of suspension), stop histamine-2 or proton pump inhibitors, and switch to intravenous formulations (if possible).[32]
- **Culture and identify fungal pathogens** whenever possible.[1,2] Disk diffusion, gradient diffusion and agar screening are less costly than the microdilution broth technique and do not require expertise to perform, but these tests do require inter-laboratory standardization[34,35] (see **Appendix 2**).
- **Provide education against self-medication**. South Asian countries have a high frequency of self-medication, which is often linked to inappropriate drug usage and high levels of antimicrobial resistance.[36,37]

Step 7: Reporting and feedback

MSGERC recommendation:[1]

1. All facilities should have a mechanism to track antifungal drug use.
2. Benchmarking antifungal use can aid in AFS work.
3. AFS programs should ideally assess patient-level outcomes where possible.
4. All AFS programs should have a mechanism for direct data feedback to prescribers.

It is important to use metrics for reporting and feedback in order to encourage institutional change and monitor intervention effectiveness.[1] Antifungal drug consumption is the most widely used metric and is usually calculated as either 'days of therapy' (DOT) or 'defined daily dose' (DDD).[1,38] It is vitally important to give direct feedback to front-line prescribers to allow them to easily interpret and apply changes to local practice.[1]

Challenges specific to Asia:

Highly variable and non-existent/immature electronic health record systems as well as an absence of internal formularies make collecting AFS metrics difficult in Asia.[39,40] A lack of funds for healthcare technology, a lack of public health government initiatives, fragmented healthcare systems, and even inconsistent power supplies[39] all create barriers. The absence of an electronic system can actually preclude the use of some metrics (eg, DOT is heavily reliant on electronic records).[1]

Expert recommendations for resource-limited settings:

- **Track antifungal drug use using standard metrics** (**Table 2**).[1]
  - DDD metrics can be calculated from a number of different sources and are easier to collect than DOT.[1] However, there are discrepancies between the DDD and the preferred daily dose for some antifungals (eg, amphotericin B, fluconazole, itraconazole), skewing can occur when loading doses are used (eg, caspofungin, voriconazole), and DDDs have limited relevance in pediatric patients due to weight-based dosing.[15,38]

- **Perform point-prevalence surveys of antifungal use** as a less resource-intensive option.[8]
  - Calculates drug exposure per admission or per patient. Prevalence is obtained by survey assessments and defined as the number of patients receiving antifungals divided by the total number of surveyed patients.[41]
- **Track patient-level outcomes** for feedback on effectiveness of AFS interventions.[1]
- **Ensure prescribers have easy access to the reports**, including feedback.[1]

Table 2

Examples of antifungal metrics and DDDs for commonly used antifungal agents[2,13]

Outcome	Examples of metrics	DDD for commonly used antifungals (DDD in grams)	
Antifungal consumption	DDD/1000 patient days DOT/1000 patient days Length of therapy	Fluconazole	0.2
Antifungal prescribing quality	No. of antifungal prescriptions reviewed No. of treatment modifications recommended Appropriate choice of antifungal agent	Isavuconazole	0.2
Diagnosis	Appropriate diagnostic test used Turnaround time for results Follow-up cultures until negative result	Itraconazole	0.2
Microbiological	Causative organisms/species Antifungal resistance Time to microbiological clearance	Posaconazole	0.3
Clinical	Incidence of IFI IFI-related mortality Hospital length of stay	Voriconazole	0.4
Cost	Antifungal prescription cost Diagnostic cost Other AFS implementation cost	Anidulafungin	0.1
		Caspofungin	0.05
		Micafungin	0.1
		Liposomal amphotericin B	-
		Flucytosine	10
		Terbinafine	0.25

AFS, antifungal stewardship; DDD, defined daily dose; DOT, days of therapy; IFI, invasive fungal infection

Appendix 1

Online resources

This table provides links to a selection of some of the most useful online resources to help with the implementation of hospital AFS programs.

Region	Organization	Resource
Global	WHO	• List of Fungal Priority Pathogens (https://iris.who.int/handle/10665/363682) • AMS program toolkit in low- and middle-income countries (https://apps.who.int/iris/handle/10665/329404) • Guidance on integrated antimicrobial stewardship activities (https://iris.who.int/handle/10665/341432)
	LIFE	Comprehensive list (with links) of published clinical guidelines for the management of fungal infections throughout the world (including Asia-Pacific) (https://en.fungaleducation.org/guidelines/)
Asia-Pacific	AFWG Asia	Antifungal-specific website affiliated with ISHAM (https://www.afwgonline.com)
	AMR&S	Multiple resources are available from this Working Group which is dedicated to advancing education and research on antimicrobial resistance in Asia (https://www.amrswg.com)
	Australasian Consensus Guidelines	Consensus guidelines for antifungal stewardship, surveillance and infection prevention in hematology-oncology patients (https://onlinelibrary.wiley.com/doi/10.1111/imj.15586)
	ISHAM	Non-governmental affiliate of the World Health Organisation representing 34 medical mycology associations (https://www.isham.org)
	Infectious Diseases Society of Taiwan	• 2016 guidelines for the use of antifungal agents in patients with invasive fungal diseases in Taiwan (https://pubmed.ncbi.nlm.nih.gov/28781150/) • 2016 guideline strategies for the use of antifungal agents in patients with hematological malignancies or hematopoietic stem cell transplantation recipients in Taiwan (https://pubmed.ncbi.nlm.nih.gov/28781151/)
	KSAT, KSID, KSHSP	Guidelines on implementing AMS programs in Korea (https://www.icjournal.org/DOIx.php?id=10.3947/ic.2021.0098)
	MOH Malaysia	Hospital AMS program guidelines (https://pharmacy.moh.gov.my/en/documents/protocol-antimicrobial-stewardship-ams-programme-healthcare-facilities-second-edition-2022.html)
	DOH Philippines	Hospital AMS program guidelines (https://drive.google.com/file/d/1s1PChMiGpaQWTC2DCdnwUqrAtn_5M9jj/view)
Europe	UK NHS	Antifungal stewardship implementation pack (https://www.england.nhs.uk/wp-content/uploads/2019/03/PSS1-meds-optimisation-trigger-5-antifungal-stewardship-implementation-pack-v7.pdf)
North America	IDSA/SHEA	Evidence-based recommendations for antifungal stewardship (https://academic.oup.com/jid/article/222/Supplement_3/S175/5880881?login=true)

AFWG, Antifungal Working Group; AMR&S, Antimicrobial Resistance & Stewardship; IDSA, Infectious Diseases Society of America; DOH, Department of Health; ISHAM, International Society for Human and Animal Mycology; KSAT, Korean Society for Antimicrobial Therapy; KSID, Korean Society of Infectious Diseases; KSHSP, Korean Society of Health-System Pharmacists; LIFE, Leading International Fungal Education; MOH, Ministry of Health; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SHEA, Society for Healthcare Epidemiology of America; UK, United Kingdom; WHO, World Health Organization.

Appendix 2

Case examples of AFS programs/interventions in Asian hospitals

Case 1: Amrita Institute of Medical Sciences, Kochi, Kerala, India[42]
Setting • 1300-bed academic tertiary care referral center with a high proportion of morbid and critical care patients **AFS team** • Undertaken by the existing AMS team • Clinical pharmacist (AFS lead) **Interventions** • Blood culture positivity for budding yeast, further identified as *Candida* spp. using an updated VITEK 2 system • Training to improve the appropriateness of antifungal therapy led by the multidisciplinary AMS team • Implementation of a candidemia-specific care bundle consisting of 5 recommendations for ideal management based on IDSA's 2016 invasive candidiasis guidelines **Measures of program effectiveness** • Plan, Do, Study, Act system • Audit of compliance to each element of the candidemia care bundle checklist • Post-prescriptive audit for antifungal appropriateness determining the 5 R's (Right indication, Right drug, Right dose, Right frequency, and Right duration) • Mortality rates • Length of stay

Case 2: Siriraj Hospital, Mahidol University, Bangkok, Thailand[35]

Setting

- A 2500-bed University Hospital with transplant center and intensive care

Study aim

- To determine whether the disk diffusion (DD) antifungal susceptibility method would facilitate effective early antifungal de-escalation and complement AFS
- Prospective study that used historical controls (patients with candidemia who underwent fluconazole susceptibility testing using the broth microdilution method)

Interventions

- DD testing was performed according to CLSI guidelines
  - Inhibition zone diameters were measured to determine susceptibility using the CLSI breakpoint
  - Disks containing 25 µg of fluconazole were used for DD testing
  - For *C. albicans, C. parapsilosis* and *C. tropicalis*, an inhibition zone diameter of ≥17 mm indicated susceptibility to fluconazole, whereas an inhibition zone of ≤13 mm indicated resistance.
  - For *C. glabrata*, an inhibition zone of ≥15 mm was considered fluconazole susceptible-dose dependent, and an inhibition zone of ≤14 mm as drug resistant.
- BMD antifungal susceptibility testing was performed using the automated Sensititre® method

Measures of program effectiveness

- Rate of antifungal de-escalation within 72h after a positive culture
- Time to appropriate antifungal de-escalation
- 14- and 30-day mortality
- Length of hospitalization
- Length of stay after the diagnosis of candidemia
- Total antifungal cost
- Treatment-related complications
- Use of empirical antifungal treatment
- Clinical response
- Duration of treatment
- *Candida* species isolated from blood cultures
- Antifungal susceptibility test result
- Time to negative culture

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