

Clinicians' challenges in managing patients with invasive fungal diseases in seven Asian countries: An Asia Fungal Working Group (AFWG) Survey

by Retno Wahyuningsih

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Clinicians' challenges in managing patients with invasive fungal diseases in seven Asian countries: An Asia Fungal Working Group (AFWG) Survey



Ban Hock Tan^{a,*}, Arunaloke Chakrabarti^b, Atul Patel^c, Mitzi Marie M. Chua^d,
Pei-Lun Sun^e, Zhengyin Liu^f, Porpon Rotjanapa^g, Ruoyu Li^h, Retno Wahyuningsihⁱ,
Methee Chayakulkeeree^j, Yee-Chun Chen^{k,l,**}, on behalf of the Asia Fungal Working Group
(AFWG)

^a Department of Infectious Diseases, Singapore General Hospital, Singapore

^b Department of Medical Microbiology, Postgraduate Institute of Medical Education & Research, Chandigarh, India

^c Department of Infectious Diseases, Vedanta Institute of Medical Sciences, India

^d Department of Microbiology and Parasitology, Cebu Institute of Medicine, Cebu City, Philippines

^e Department of Dermatology, Chang Memorial Hospital, Linkou Branch and College of Medicine, Chang Gung University, Taoyuan, Taiwan

^f Department of Infectious Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

^g Division of Infectious Diseases, Ramathibodi Hospital, Bangkok, Thailand

^h Department of Dermatology, Peking University First Hospital, Research Centre for Medical Mycology, Peking University, Beijing, China

ⁱ Department of Parasitology, Faculty of Medicine Universitas Indonesia, and Department of Parasitology, Faculty of Medicine Universitas Kristen Indonesia, Jakarta, Indonesia

^j Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

^k Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan

^l National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Zhunan, Taiwan

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ABSTRACT

Background: Invasive fungal diseases (IFD) are a serious threat, but physicians in Asia lack access to many advanced diagnostics in mycology. It is likely that they face other impediments in the management of IFD. A gap analysis performed to understand the challenges Asian physicians faced in medical mycology. **Methods:** The Asia Fungal Working Group (AFWG) conducted a web-based survey on management practices for IFD among clinicians in China, India, Indonesia, Philippines, Singapore, Taiwan and Thailand. **Findings:** Among 292 respondents, 51.7% were infectious disease (ID) specialists. Only 37% of respondents had received formal training in medical mycology. They handled only around 2–4 proven cases of each fungal infection monthly, with invasive candidiasis the most common. For laboratory support, the majority had access to direct microscopy (96%) and histopathology (87%), but galactomannan and azole levels were available to 60% and 25% of respondents, respectively. The majority (84%) used clinical parameters for treatment response monitoring, and 77% followed the Infectious Diseases Society of America guidelines. The majority (84%) did not use the services of an ID physician. Where febrile neutropenia was concerned, 74% of respondents used the empirical approach. Only 30% had an antifungal stewardship program in their hospital. Eighty percent could not use preferred antifungals because of cost. **Interpretation:** The survey identified inadequacies in medical mycology training, non-culture diagnostics, access to antifungal drugs, and local guidelines as the major gaps in the management of IFDs in Asian countries. These gaps are targets for improvement.

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* Corresponding author at: Department of Infectious Diseases, Singapore General Hospital, 20 College Road, Singapore 169856, Singapore.

** Corresponding author at: Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan.

E-mail addresses: tan.ban.hock@singhealth.com.sg (B.H. Tan), yeechunchen@gmail.com (Y.-C. Chen).

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Research in context

Evidence before this study

The global impact of invasive fungal diseases (IFDs) on morbidity and mortality is significant. With limited resources, clinicians in Asian countries face significant challenges in diagnosing and treating IFDs. A gap analysis is needed to identify the gaps and needs for improving the outcomes of IFDs in this region.

Added value of this study

This is the first multinational clinicians' survey on mycology practice patterns. IFDs are not commonly diagnosed among hospitalized patients handled by the respondents of the survey, which likely relates to diagnostic and awareness limitations. The majority of clinicians depend on conventional approaches, such as microscopy, culture, histopathology and imaging, as modes of diagnosis. Due to the lack of advanced diagnostic techniques, there is a tendency to employ the empirical treatment approach when managing IFDs.

Implications of all the available evidence

Major gaps identified include a lack of formal training in medical mycology, inadequate access to advanced diagnostics and antifungal agents, and a paucity of local guidelines. In the area of training, professional bodies with an educational focus, such as the Asia Fungal Working Group (AFWG), should play a more active role, but funding support is crucial. Other challenges include capacity-building in local mycology laboratories and the development of evidence-based clinical practice guidelines in medical mycology for local use.

Introduction

Fungal pathogens receive scant attention in Asian countries, despite posing a significant threat to human health, food biosecurity and biodiversity (Anon, 2017). Recognition of the threat of invasive fungal disease (IFD) is still evolving among clinicians, microbiologists, hospital administrators and funding agencies in those countries. Clinicians' knowledge of and ability to diagnose fungal diseases play a key role in raising awareness of the impact of fungi on human health.

Asia might have the largest burden of fungal disease in the world, as it has more than half the world's population and fungi thrive in a tropical/subtropical environment. Studies from Asia suggest that the incidence rates of candidemia and possibly other IFDs are relatively high compared with international data (Tan et al., 2015; Chakrabarti et al., 2015; Chen et al., 2014, 2003; Tang et al., 2015). Several large series on paranasal mold infections come from India (Chakrabarti et al., 2009; Panda et al., 1998; Murthy et al., 2001). The incidence, in fact, may be higher than currently reported. Taiwanese investigators found that the incidence of invasive aspergillosis (IA) rose with a rise in the use of the galactomannan (GM) test (Sun et al., 2016). Yet, outside the most advanced economies, access to diagnostic testing is limited (Chindamporn et al., 2018). The incidence of chronic pulmonary aspergillosis (CPA) – a known late consequence of pulmonary tuberculosis (PTB) – is also thought to be high, given that PTB is common in many parts of Asia (Denning et al., 2011). Japanese investigators have recognized CPA as a problem of some urgency in Japan “due to the many aged people with past history of tuberculosis” (Saito et al., 2012).

Interesting case reports/series on IFD in Asia (Norlinah et al., 2007; Kawakami et al., 2017; Tang et al., 2016; Yoon et al., 2007) describe challenges in diagnosis and management, and we suspect that physicians in Asia face multiple challenges in the care of patients with IFD, but there are no objective data on the nature and extent of these

challenges. Thus, the Asia Fungal Working Group (AFWG) performed this survey to understand the current status of clinical practice in the diagnosis and management of IFDs, identify gaps in managing IFD patients, and explore targets to achieve to close the gaps.

Materials and methods

The study group

The AFWG, developed under the International Society for Human and Animal Mycology (ISHAM), is a non-profit working group of Asian mycologists and infectious disease (ID) specialists. The AFWG aims to improve the diagnosis and management of IFDs in Asia through education and research.

Web-based survey

To understand the current practices of clinicians handling IFDs, as well as the problems they face, the AFWG designed and conducted an online survey in 2016. Clinicians from seven Asian countries (China, India, Indonesia, Philippines, Singapore, Taiwan and Thailand) – countries in which the AFWG board had a country representative – were invited to participate. A 22-item questionnaire was developed covering questions on epidemiology, diagnostics and management of IFDs, and individual training in medical mycology (Appendix 1). AFWG country representatives were responsible for inviting clinicians in their respective countries to complete the survey. The survey was open to all clinicians managing IFDs, in particular doctors from the fields of ID, critical care, transplant medicine, hematology and oncology. The AFWG country representative sent invitation letters detailing the purpose of the study both individually to clinicians and through the national/local societies for ID, hematology and oncology, as well as pulmonary and/or critical care. Non-duplication of respondents was verified by a manual check for unique IP addresses. The workflow of the survey is shown in Appendix 2.

Data analysis

Weber Shandwick Hong Kong, a professional consulting firm, programmed and hosted the online survey, and was responsible for data capture from the participants. The data sets were scrutinized for missing or discrepant data; discrepant data were excluded. Finally, the authors analyzed the data. Intergroup differences were compared using the Chi-Square test or Fisher exact test for categorical variables, and the *t* test or Mann-Whitney U test for continuous variables based on their normality, as appropriate. When multiple groups were compared, one-way ANOVA test was used. *P* values lower than 0.05 were considered statistically significant. All analyses were conducted using the SAS software 9.4 (SAS Institute, Cary, NC, USA).

Ethics

No institutional regulatory board approval was necessary for this voluntary survey of clinicians.

Results

Respondent demographics

Over a period of 6 months (May to October 2016), 292 completed surveys were received, representing 292 individual physicians from the seven countries (in rank order): India (n = 109), the Philippines (74), China (34), Taiwan (27), Indonesia (17), Singapore (17) and Thailand (14) (Table 1). ID physicians made up

Table 1
Country comparison of survey responses from physicians in 7 Asian countries: characteristics of respondents and their training experiences.

Determinants	Overall [n = 292]	China [n = 34]	India [n = 109]	Indonesia [n = 17]	Philippines [n = 74]	Singapore [n = 17]	Taiwan [n = 27]	Thailand [n = 14]
Specialty								
ID physician	151/292 (51.7%)	22/34 (64.7%)	23/109 (21.1%)	6/17 (35.3%)	52/74 (70.3%)	11/17 (64.7%)	26/27 (96.3%)	11/14 (78.6%)
Hematologist/oncologist	22/292 (7.5%)	4/34 (11.8%)	10/109 (9.2%)	1/17 (5.9%)	3/74 (4.1%)	1/17 (5.6%)	1/27 (3.7%)	2/14 (14.3%)
Transplant physician or surgeon	8/292 (2.7%)	0	4/109 (3.7%)	1/17 (5.9%)	1/74 (1.4%)	2/17 (11.8%)	0	0
Intensivist/chest physician	73/292 (25.0%)	0	58/109 (53.2%)	3/17 (17.6%)	9/74 (12.2%)	3/17 (17.6%)	0	0
Other	38/292 (8.2%)	8/34 (23.5%)	14/109 (12.8%)	6/17 (35.3%)	9/74 (12.2%)	0	0	1/14 (7.1%)
Other	10/292 (3.4%)	1/34 (2.9%)	6/109 (5.5%)	3/17 (17.6%)	0	0	0	0
Internal medicine/ internist	14/292 (4.8%)		3/109 (2.8%)	1/17 (5.9%)	9/74 (12.2%)			1/14 (7.1%)
Clinical microbiologist	6/292 (2.1%)		4/109 (3.7%)	2/17 (11.8%)				
Permatologist	8/292 (2.7%)	7/34 (20.6%)	1/109 (0.9%)					
How many years have you practiced as a specialist?								
<5 years	98/292 (33.6%)	7/34 (20.6%)	28/109 (25.7%)	4/17 (23.5%)	36/74 (48.7%)	7/17 (41.2%)	7/27 (25.9%)	9/14 (64.3%)
5–9 years	50/292 (17.1%)	4/34 (11.8%)	21/109 (19.3%)	1/17 (5.9%)	15/74 (20.3%)	4/17 (23.4%)	4/27 (14.8%)	1/14 (7.1%)
10–14 years	52/292 (17.8%)	5/34 (14.7%)	25/109 (22.9%)	3/17 (17.7%)	8/74 (10.8%)	1/17 (5.9%)	6/27 (22.2%)	4/14 (28.6%)
>15 years	92/292 (31.5%)	18/34 (52.9%)	35/109 (32.1%)	9/17 (52.9%)	15/74 (20.3%)	5/17 (29.4%)	10/27 (37.0%)	0
How many years have you practiced as a specialist?								
By specialty	Overall N = 292			ID physicians, n = 151			Non-ID physicians, n = 141	
<5 years	98/292 (33.6%)			56/151 (37.1%)			42/141 (29.8%)	
5–9 years	50/292 (17.1%)			30/151 (19.9%)			20/141 (14.2%)	
10–14 years	52/292 (17.8%)			20/151 (13.3%)			32/141 (22.7%)	
≥15 years	92/292 (31.5%)			45/151 (29.8%)			47/141 (33.3%)	
	Overall [N = 292]	China [n = 34]	India [n = 109]	Indonesia [n = 17]	Philippines [n = 74]	Singapore [n = 17]	Taiwan [n = 27]	Thailand [n = 14]
Have you attended course(s)/training specific training on fungal infections such as CBS, training at mycology laboratory, etc?								
Yes, <1 month	74/292 (25.3%)	11/34 (32.4%)	12/109 (11.0%)	1/17 (5.9%)	25/74 (33.8%)	3/17 (17.7%)	18/27 (66.7%)	4/14 (28.6%)
Yes, 1–3 months	12/292 (4.1%)	3/34 (8.8%)	2/109 (1.8%)	0	3/74 (4.1%)	0	3/17 (11.1%)	1/14 (7.1%)
Yes, 4–6 months	3/292 (1.0%)	2/34 (5.9%)	0	0	0	1/17 (5.9%)	0	0
Yes, >6 months	20/292 (6.8%)	5/34 (14.7%)	4/109 (3.7%)	4/17 (23.5%)	3/74 (4.1%)	0	2/27 (7.4%)	2/14 (14.3%)
No	183/292 (62.7%)	13/34 (38.2%)	91/109 (83.5%)	12/17 (70.6%)	43/74 (58.1%)	13/17 (76.5%)	4/27 (14.8%)	7/14 (50.0%)
Have you attended course(s)/training specific training on fungal infections such as CBS, training at mycology laboratory, etc?								
	Overall N = 292			ID physicians, n = 151			Non-ID physicians, n = 141	
Yes, <1 month	74/292 (25.3%)			60/151 (39.7%)			14/141 (9.9%)	
Yes, 1–3 months	12/292 (4.1%)			10/151 (6.6%)			2/141 (1.4%)	
Yes, 4–6 months	3/292 (1.0%)			2/151 (1.3%)			1/141 (0.7%)	
Yes, >6 months	20/292 (6.8%)			11/151 (7.3%)			9/141 (6.4%)	
No	183/292 (62.7%)			68/151 (45.0%)			115/141 (81.6%)	
Have you attended course(s)/training specific training on fungal infections such as CBS, training at mycology laboratory, etc?								
	Overall N = 292			35% of specialty practice <5 years	Length of specialty practice 5–14 years		Length of specialty practice ≥15 years	
Yes, <1 month	74/292 (25.3%)		22/98 (22.4%)		27/102 (26.5%)		25/92 (27.2%)	
Yes, 1–3 months	12/292 (4.1%)		3/98 (3.1%)		6/102 (6.0%)		3/92 (3.2%)	
Yes, 4–6 months	3/292 (1.0%)		1/98 (1.0%)		0		2/92 (2.2%)	
Yes, >6 months	20/292 (6.8%)		4/98 (4.1%)		6/102 (6.0%)		10/92 (10.9%)	
No	183/292 (62.7%)		68/98 (69.4%)		63/102 (62.0%)		52/92 (56.5%)	
Please rate the education/training in clinical mycology in your medical school and in your trainee years								
	In medical school			During trainee years				
	Overall N = 290	ID physicians, n = 150	Non-ID physicians, n = 140	Overall N = 274	ID physicians, n = 143	Non-ID physicians, n = 131		
Poor	155/290 (53.4%)	82/150 (54.7%)	73/140 (52.1%)	95/274 (34.7%)	46/143 (32.2%)	49/131 (37.4%)		
Adequate	116/290 (40.0%)	60/150 (40.0%)	56/140 (40.0%)	126/274 (46.0%)	71/143 (49.7%)	55/131 (42.0%)		
Excellent	12/290 (4.1%)	5/150 (3.3%)	7/140 (5.0%)	24/274 (8.8%)	14/143 (9.8%)	10/131 (7.6%)		
N/A	7/290 (2.4%)	3/150 (2.0%)	4/140 (2.9%)	29/274 (10.6%)	12/143 (8.4%)	17/131 (13.0%)		
	Overall [N = 290]	China[n = 34]	India[n = 108]	Indonesia[n = 17]	Philippines[n = 73]	Singapore[n = 17]	Taiwan[n = 27]	Thailand[n = 14]
Please rate the education/training in clinical mycology in your medical school								
Poor	155/290 (53.4%)	13/34 (38.2%)	65/108 (60.2%)	8/17 (47.1%)	31/73 (42.5%)	14/17 (82.4%)	20/27 (74.1%)	4/14 (28.6%)
Adequate	116/290 (40.0%)	15/34 (44.1%)	39/108 (36.1%)	8/17 (47.1%)	37/73 (50.7%)	3/17 (17.7%)	6/27 (22.2%)	8/14 (57.1%)
Excellent	12/290 (4.1%)	2/34 (5.9%)	3/108 (2.8%)	0	5/73 (6.9%)	0	1/27 (3.7%)	1/14 (7.1%)
N/A	7/290 (2.4%)	4/34 (11.8%)	1/108 (0.9%)	1/17 (10.6%)	0	0	0	1/14 (7.1%)

	Overall [N = 274]	China[n = 33]	India[n = 100]	Indonesia[n = 16]	Philippines[n = 68]	Singapore[n = 17]	Taiwan[n = 26]	Thailand[n = 14]	
1	Please rate the education/training in clinical mycology in your trainee years								
Poor	95/274 (34.7%)	6/33 (18.2%)	38/100 (38.0%)	6/16 (37.5%)	21/68 (30.9%)	12/17 (70.6%)	10/26 (38.5%)	2/14 (14.3%)	
Adequate	126/274 (46.0%)	20/33 (60.6%)	38/100 (38.0%)	6/16 (37.5%)	38/68 (55.9%)	4/17 (23.5%)	12/26 (46.2%)	8/14 (57.1%)	
Excellent	24/274 (8.8%)	3/33 (9.1%)	12/100 (12.0%)	1/16 (6.3%)	3/68 (4.4%)	1/17 (5.9%)	2/26 (7.7%)	2/14 (14.3%)	
N/A	29/274 (10.6%)	4/33 (12.1%)	12/100 (12.0%)	3/16 (18.8%)	6/68 (8.8%)	0	2/26 (7.7%)	2/14 (14.3%)	

ID, infectious disease; N/A, not applicable.

51.7% (151/292) of the respondents, followed by intensivists/chest physicians (73, 25.0%), and hematologists/oncologists (22, 7.5%). The survey covered both young and experienced clinicians; 98 (34%) of the survey participants had practiced in their field/specialty for <5 years, and 92 (32%) for more than 15 years.

Formal training in medical mycology

Overall, 62.7% (183/292) of respondents had not attended formal training in medical mycology (Table 1). The proportion of physicians who had not attended medical mycology training courses was significantly higher amongst non-ID physicians (115/141, 81.6%; $p < 0.0001$) than ID physicians (68/151, 45.0%). Fifty-three percent (155/290) of the respondents rated as poor the quality of medical mycology training that they had received in medical school, while 34.7% (95/274) assessed as poor the training received during their trainee years ($p < 0.0001$).

Practice experience

Of 141 respondents who were not ID physicians, 104 (73%) managed IFD themselves, a figure that included the majority of hematologists/oncologists (18/22, 82%) and intensivists/chest physicians (64/73, 87%).

With regard to suspected/confirmed aspergillosis in the intensive care unit (ICU), the referral pattern was consistent – with only 18% of hematologists/oncologists and 12% of intensivists/chest physicians asking for an ID consult. However, in this specific setting, 75% of transplant physicians/surgeons indicated that they referred to an ID physician. The estimated numbers of cases seen for each IFD are shown in Table 2. Based on the proportion of respondents managing two or more proven cases per month, invasive candidiasis was encountered most commonly (by 90.1% of respondents), followed by IA (71.9%), cryptococcosis (68.7%), other yeast infection (68.0%), pneumocystosis (66.8%), CPA (61.6%), allergic bronchopulmonary aspergillosis (64.6%) and invasive mucormycosis (58.8%). Fusariosis, scedosporiosis, penicilliosis and histoplasmosis appeared less common.

Laboratory support in management

The majority of respondents had access to microscopy (279/292, 95.5%) and histopathology (255/292, 87.3%) for establishing the diagnosis of fungal infections (Figure 1). Of advanced biomarker tests, the most commonly accessible was the GM assay (177/292, 60.7%), followed by the beta-D-glucan (62/292, 21.2%) and *Candida* antigen assays (54/292, 18.5%). In general, molecular-based diagnostics (i.e. polymerase chain reaction [PCR] assays) were less widely available than microscopy and histopathology. Eighty-nine of 292 (30.5%) respondents used the *Pneumocystis jirovecii* PCR assay, followed by *Candida* (13.7%), *Aspergillus* (14.4%) and panfungal PCR assays (7.9%).

To monitor response to therapy, the majority of respondents used clinical parameters (238/292, 81.5%), imaging (216, 74.0%) and blood cultures (215, 73.6%). Around one in three respondents

(99/292, 33.9%) used the GM assay. Therapeutic drug monitoring (TDM) during azole therapy was used by 25.7% (75/292) of respondents; 62.7% (47/75) of them used TDM more than once during a patient's course of treatment and the remaining 37.3% (28/75) performed it only once.

Treatment guidelines

The majority (11) respondents (227/292, 77.7%) stated that they followed the Infectious Diseases Society of America (IDSA) guidelines on the management of IFDs (Table 3), and 25.3% of respondents used the European Society of Clinical Microbiology and Infectious Disease (ESCMID) guidelines (multiple answers permitted for this question). The proportion of respondents using IDSA guidelines ranged from 96.3% (26/27 respondents) in Taiwan to 47.1% (8/17) in Indonesia. Twenty-six percent (76/292) of all respondents reported referring to national/or local guidelines, ranging from 76.5% (26/34) in China to 5.9% (1/17) in Singapore.

Compared with non-ID physicians, higher proportions of ID physicians followed IDSA guidelines (67.4% [95/141] vs 87.4% [132/151], respectively; $p < 0.001$), ESCMID guidelines (10.6% [15/141] vs 39.1% [59/151]; $p < 0.0001$) and national guidelines (19.2% [27/141] vs 32.5% [49/151]; $p = 0.0096$). On the other hand, more non-ID physicians followed institutional/unit guidelines (54/141, 38.3%) than ID physicians (21/151, 13.9%; $p < 0.0001$).

Antifungal strategies

The antifungal treatment strategies by patient population or disease entity are provided in Table 3. The proportion of respondents using antifungal prophylaxis in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) and those with acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) exceeded 50% in India, Singapore and Taiwan (Table 3). Hematologists/oncologists were more likely than other specialists to use antifungal prophylaxis in patients with AML/MDS (15/22, 68.2%; Figure 2) and those undergoing allo-HSCT (13/22, 61.9%). Antifungal prophylaxis against candidiasis/candidemia in the ICU was much less commonly practiced – no respondent from Taiwan or Thailand used it, and only small numbers of respondents from the other countries used it (Table 3). Empirical therapy was the main strategy in febrile neutropenia (67.1% of all respondents), used by more than 70% of ID physicians, hematologists/oncologists, and intensivists/chest physicians (Figure 3). The approach to managing patients with suspected invasive candidiasis in the ICU was almost equally divided between a diagnostic-driven (47.5%) and an empirical (46.3%) approach (Table 3). The majority of respondents (269/292, 92.1%) practiced source control, such as removal of central lines or urinary catheters, and 58.6% (171/292) of respondents attempted surgical debridement of infected tissues while managing IFDs (data not shown). Finally, 30.1% (88/292) of respondents indicated their institution had an antifungal stewardship program in place, ranging from 11.8% (Singapore and Indonesia) to 64.3% (Thailand) (Table 3).

Table 2
Distribution of numbers of cases with proven invasive fungal diseases handled by respondents per month.^a

Fungus	Overall [n = 292]	China [n = 34]	India [n = 109]	Indonesia [n = 17]	Philippines [n = 74]	Singapore [n = 17]	Taiwan [n = 27]	Thailand [n = 14]
Yeasts								
Candidiasis								
0–6 cases/month	29/292 (9.9%)	2/34 (5.9%)	12/109 (11.0%)	2/17 (11.8%)	10/74 (13.5%)	3/17 (17.6%)	0/27	0/14
2–4 cases/month	217/292 (74.3%)	27/34 (79.4%)	82/109 (75.2%)	11/17 (64.7%)	56/74 (75.7%)	14/17 (82.4%)	15/27 (55.6%)	12/14 (85.7%)
≥ 5 cases/month	46/292 (15.8%)	5/34 (14.7%)	15/109 (13.8%)	4/17 (23.5%) ^d	8/74 (10.8%)	0/17	12/27 (44.4%) ^d	2/14 (14.3%)
Cryptococcosis								
0–6 cases/month	91/291 (31.3%)	6/34 (17.6%)	46/109 (42.2%)	6/16 (37.5%)	24/74 (32.4%)	4/17 (23.5%)	5/27 (18.5%)	0/14
2–4 cases/month	184/291 (63.2%)	24/34 (70.6%)	61/109 (56.0%)	9/16 (56.3%)	42/74 (56.8%)	13/17 (76.5%)	22/27 (81.5%)	13/14 (92.9%)
≥ 5 cases/month	16/291 (5.5%)	4/34 (11.8%)	2/109 (1.8%)	1/16 (6.3%)	8/74 (10.8%)	0/17	0/27	1/14 (7.1%)
Other yeasts								
0–6 cases/month	93/291 (32.0%)	4/34 (11.8%)	43/108 (39.8%)	9/17 (52.9%)	24/74 (32.4%)	4/17 (23.5%)	8/27 (29.6%)	1/14 (7.1%)
2–4 cases/month	183/291 (62.9%)	24/34 (70.6%)	58/108 (53.7%)	8/17 (47.1%)	48/74 (64.9%)	13/17 (76.5%)	19/27 (70.4%)	13/14 (92.9%)
≥ 5 cases/month	15/291 (5.2%)	6/34 (17.6%) ^c	7/108 (6.5%)	0/17	2/74 (2.7%)	0/17	0/27	0/14
Pneumocystosis								
0–6 cases/month	97/292 (33.2%)	7/34 (20.6%)	42/109 (38.5%)	8/17 (47.1%)	30/74 (40.5%)	4/17 (23.5%)	6/27 (22.2%)	0/14
2–4 cases/month	162/292 (55.5%)	23/34 (67.6%)	61/109 (56.0%)	9/17 (52.9%)	30/74 (40.5%)	11/17 (64.7%)	18/27 (66.7%)	10/14 (71.4%)
≥ 5 cases/month	33/292 (11.3%)	4/34 (11.8%)	6/109 (5.5%)	0/17	14/74 (18.9%)	2/17 (11.8%)	3/27 (11.1%)	4/14 (28.6%)
Molds								
Aspergillosis								
0–6 cases/month	82/292 (28.1%)	7/34 (20.6%)	30/109 (27.5%)	6/17 (35.3%)	29/74 (39.2%)	4/17 (23.5%)	4/27 (14.8%)	2/14 (14.3%)
2–4 cases/month	197/292 (67.5%)	24/34 (70.6%)	70/109 (64.2%)	11/17 (64.7%)	44/74 (59.5%)	13/17 (76.5%)	23/27 (85.2%)	12/14 (85.7%)
≥ 5 cases/month	13/292 (4.5%)	3/34 (8.8%) ^c	9/109 (8.3%) ^c	0/17	1/74 (1.4%)	0/17	0/27	0/14
ABPA								
0–1 cases/month	132/291 (45.4%)	7/34 (20.6%)	52/109 (47.7%)	12/16 (75.0%)	42/74 (56.8%)	6/17 (35.3%)	9/27 (33.3%)	4/14 (28.6%)
2–4 cases/month	146/291 (50.2%)	25/34 (73.5%)	47/109 (43.1%)	4/16 (25.0%)	32/74 (43.2%)	11/17 (64.7%)	17/27 (63.0%)	10/14 (71.4%)
≥ 5 cases/month	13/291 (4.5%)	2/34 (5.9%)	10/109 (9.2%) ^c	0	0	0	1/27 (3.7%)	0
Chronic pulmonary aspergillosis								
0–1 cases/month	112/292 (38.4%)	6/34 (17.6%)	45/109 (41.3%)	11/17 (64.7%)	35/74 (47.3%)	4/17 (23.5%)	7/27 (25.9%)	4/14 (28.6%)
2–4 cases/month	175/292 (59.9%)	27/34 (79.4%)	60/109 (55.0%)	6/17 (35.3%)	39/74 (52.7%)	13/17 (76.5%)	20/27 (74.1%)	10/14 (71.4%)
≥ 5 cases/month	5/292 (1.7%)	1/34 (2.9%)	4/109 (3.7%)	0	0	0	0	0
Mucormycosis								
0–1 cases/month	120/291 (41.2%)	8/34 (23.5%)	41/109 (37.6%)	13/16 (81.3%)	42/74 (56.8%)	6/17 (35.3%)	8/27 (29.6%)	2/14 (14.3%)
2–4 cases/month	164/291 (56.4%)	24/34 (70.6%)	63/109 (57.8%)	3/16 (18.8%)	32/74 (43.2%)	11/17 (64.7%)	19/27 (70.4%)	12/14 (85.7%)
≥ 5 cases/month	7/291 (2.4%)	2/34 (5.9%)	5/109 (4.6%)	0	0	0	0	0
Fusariosis								
0–1 cases/month	162/291 (55.7%)	10/34 (29.4%)	70/109 (64.2%)	13/16 (81.3%)	49/74 (66.2%)	6/17 (35.3%)	11/27 (40.7%)	3/14 (21.4%)
2–4 cases/month	126/291 (43.3%)	22/34 (64.7%)	38/109 (34.9%)	3/16 (18.8%)	25/74 (33.8%)	11/17 (64.7%)	16/27 (59.3%)	11/14 (78.6%)
≥ 5 cases/month	3/291 (1.0%)	2/34 (5.9%) ^b	1/109 (0.9%)	0	0	0	0	0
Scedosporiosis								
0–1 cases/month	164/291 (56.4%)	9/34 (26.5%)	71/109 (65.1%)	13/16 (81.3%)	51/74 (68.9%)	6/17 (35.3%)	11/27 (40.7%)	3/14 (21.4%)
2–4 cases/month	124/291 (42.6%)	23/34 (67.6%)	37/109 (33.9%)	3/16 (18.8%)	23/74 (31.1%)	11/17 (64.7%)	16/27 (59.3%)	11/14 (78.6%)
≥ 5 cases/month	3/291 (1.0%)	2/34 (5.9%) ^b	1/109 (0.9%)	0	0	0	0	0
Black mycelial fungi								
0–1 cases/month	162/291 (55.7%)	10/34 (29.4%)	69/109 (63.3%)	13/16 (81.3%)	51/74 (68.9%)	6/17 (35.3%)	11/27 (40.7%)	2/14 (14.3%)
2–4 cases/month	125/291 (43.0%)	21/34 (61.8%)	39/109 (35.8%)	3/16 (18.8%)	23/74 (31.1%)	11/17 (64.7%)	16/27 (59.3%)	12/14 (85.7%)
≥ 5 cases/month	4/291 (1.4%)	3/34 (8.8%) ^c	1/109 (0.9%)	0	0	0	0	0
Dimorphic								
Penicilliosis								
0–6 cases/month	153/291 (52.6%)	6/34 (17.6%)	70/109 (64.2%)	13/16 (81.3%)	49/74 (66.2%)	6/17 (35.3%)	7/27 (25.9%)	2/14 (14.3%)
2–4 cases/month	131/291 (45.0%)	23/34 (67.6%)	38/109 (34.9%)	3/16 (18.8%)	25/74 (33.8%)	11/17 (64.7%)	20/27 (74.1%)	11/14 (78.6%)
≥ 5 cases/month	7/291 (2.4%)	5/34 (14.7%) ^d	1/109 (0.9%)	0	0	0	0	1/14 (7.1%)
Histoplasmosis								
0–6 cases/month	147/291 (50.5%)	8/34 (23.5%)	66/109 (60.6%)	12/16 (75.0%)	42/74 (56.8%)	6/17 (35.3%)	11/27 (40.7%)	2/14 (14.3%)
2–4 cases/month	141/291 (48.5%)	23/34 (67.6%)	43/109 (39.4%)	4/16 (25.0%)	32/74 (43.2%)	11/17 (64.7%)	16/27 (59.3%)	12/14 (85.7%)
≥ 5 cases/month	3/291 (1.0%)	3/34 (8.8%) ^c	0	0	0	0	0	0

ABPA, allergic bronchopulmonary aspergillosis.

^a 32 shown were the proportion of respondents in each category, 0-1 case per month, 2-4 cases per month, 5 or more cases per month.

^b P < 0.05.

^c P < 0.01.

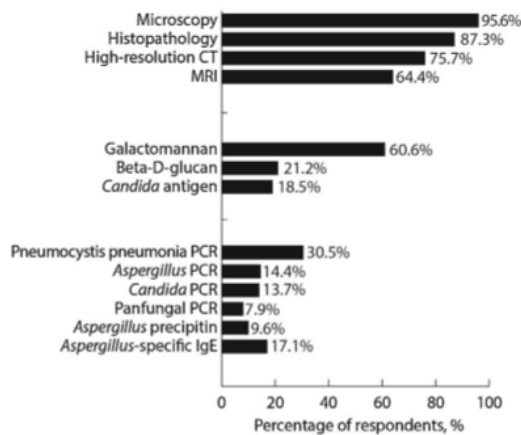
^d P < 0.001.

Constraints on the use of antifungal agents

Respondents were asked whether affordability, institutional policy, national availability or health insurance policy regulations ever prevented them using their preferred choice of antifungal agent. Among all respondents, “Patient cannot afford” was the most frequently selected reason for not using the preferred antifungal drug (233/292, 79.8%) (Figure 4). A country comparison

shows this was the most common reason selected by physicians in India (102/109, 93.6%), the Philippines (67/74, 90.5%), Singapore (15/17, 88.2%), China (24/34, 71.0%) and Thailand (9/14, 64.3%). Taiwanese physicians most commonly (21/27, 77.8%) cited insurance restrictions (non-coverage) as the reason for not using their preferred antifungal. Physicians from China (17/34, 50.0%), Indonesia (8/17, 47.1%) and the Philippines (41/74, 55.4%) were more likely to select “Drug not available in your country” as a

A.



B.

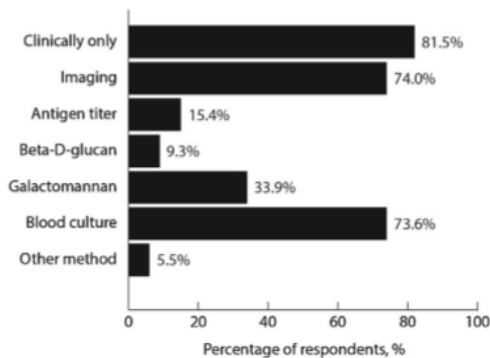


Figure 1. The accessibility of laboratory diagnostics for management of patients with fungal infections (A) and approaches for monitoring patient response (B).

barrier to preferred drug use than the other four countries. Drug unavailability was selected by 25.9% (7/27) of respondents in Taiwan.

Strategies to improve the management of IFD

The majority of respondents felt that training, diagnostics, guidelines, drug availability and research were important to improve the management of IFDs in the region. Of these, the top three strategies were: improvement in diagnostic tests in the hospital (75.3% of respondents); country-specific training courses (70.8%); and development of institutional or national guidelines (69.8%) (Table 4). Overall, 59.1% of respondents considered AFWG-initiated training courses a helpful strategy, ranging from 42.9% in Thailand to 76.5% in Indonesia.

Discussion

This survey represents a first attempt to understand how clinicians managed IFDs in seven Asian countries. The survey demonstrated gaps in training, limitations in diagnostic modalities, difficulties in accessing antifungal drugs and a lack of local

guidelines as major impediments to the appropriate management of IFD.

The majority of survey respondents had not attended formal training in mycology. The meaning of “formal training” had been defined in the survey, so it is unlikely that this question was misunderstood. More than half the respondents rated the quality of medical mycology training in medical school as “poor”. Training in mycology in the postgraduate years was rated as “excellent” by a minority of respondents. Even among ID physicians, a minority had had formal training in medical mycology (Table 1). Taken together, these findings suggest that medical mycology had not been adequately emphasized in the training of doctors and specialists in the respondents’ countries.

This survey also suggests that respondents lacked access to advanced diagnostics in medical mycology. The majority had access to microscopy, histopathology and imaging and likely used these as the most common modes of IFD diagnosis. These findings are corroborated by the results of a survey of laboratory practices for the diagnosis of IFD in the same seven Asian countries (Chindamporn et al., 2018). We suspect that this contributes to the very small number of proven IFD cases seen per month by the respondents. Biopsies, which are necessary before histopathology can help secure the diagnosis, are often precluded by thrombocytopenia in a group of patients (those with hematological malignancies) at high risk of IFDs. As noted before, Taiwanese investigators found that the incidence of IPA rose with increased use of the GM assay (Sun et al., 2016).

It is noteworthy that 60.7% of respondents used the GM assay, when this assay was reported to be available in only 22.8% of the laboratories surveyed and was performed once (18.8%) or twice per week (46.9%) (Chindamporn et al., 2018). In a similar vein, 25.7% of clinicians used azole TDM, while only 8.7% (21/241) of laboratories previously surveyed performed azole TDM (Chindamporn et al., 2018). These discrepancies suggest that clinicians are sending their specimens outside their hospital, a situation that raises concern for turnaround times, especially for centers managing challenging patients such as those with hematological malignancies and those undergoing transplants. In the survey, more than three-quarters of the respondents reported following the IDSA guidelines and about a quarter reported following the ESCMID guidelines. Taken together with the data on the use and availability of advanced diagnostics, it seems reasonable to infer that, in today’s internet age, knowing what is internationally recommended is not difficult. To comply with guidelines, however, many likely stretched themselves to use tests not available in-house. The survey did not capture the ease or regularity with which these “send-out” tests were used. Nevertheless, there are problems, such as administrative hurdles, inherent in “send-out” tests. These problems, plus the expectation of a delayed result, may be barriers to the use of these tests in usual care.

The survey suggested that the frequency at which respondents managed cases of CPA was not much more than the frequency at which they managed cases of mucormycosis (Table 2). Recall bias may play a role, with the unusual cases of mucormycosis being easier to recall. It may also represent under-diagnosis of CPA. Denning et al. estimated that, given high rates of tuberculosis in many parts of Asia, the rates of CPA should be correspondingly high (Denning et al., 2011). This may reflect lack of knowledge, or lack of access to diagnostics, as a serological/microbiological test is often required in support of the diagnosis of CPA (Denning et al., 2016). Page et al., for example, emphasized that antibody testing was “central” to the diagnosis of these conditions (Page et al., 2015), and antibody testing not available in the majority of the centers.

It is striking that only a minority of non-ID respondents referred patients with IFDs to ID physicians, despite their view that training in medical mycology had been suboptimal. An increasing body of

Table 3
Country comparison of survey responses from physicians in 7 Asian countries: treatment guidelines, antifungal strategy and selection of antifungal agents.

Overall	China	India	Indonesia	Philippines	Singapore	Taiwan	Thailand
What are your program's/department's management approaches for allo-HSCT recipients							
Prophylaxis	95/161 (59.0%)	9/19 (47.4%)	39/59 (66.1%)	0	18/38 (47.4%)	6/8 (75.0%)	19/20 (95.0%)
Diagnostic driven	35/161 (21.7%)	4/19 (21.0%)	10/59 (16.9%)	4/6 (66.7%)	11/38 (28.9%)	1/8 (12.5%)	0
Empirical	31/161 (19.3%)	6/19 (31.6%)	10/59 (16.9%)	2/6 (33.3%)	9/38 (23.7%)	1/8 (12.5%)	2/11 (18.2%)
What are your program's/department's management approaches for patients with AML/MDS							
Prophylaxis	88/202 (43.6%)	6/20 (30.0%)	48/74 (64.9%)	3/8 (37.5%)	11/56 (19.6%)	6/9 (66.7%)	12/22 (54.5%)
Diagnostic driven	51/202 (25.2%)	6/20 (30.0%)	14/74 (18.9%)	3/8 (37.5%)	18/56 (32.1%)	2/9 (22.2%)	1/22 (4.5%)
Empirical	63/202 (31.2%)	8/20 (40.0%)	12/74 (16.2%)	2/8 (25.0%)	27/56 (48.2%)	1/9 (11.1%)	9/22 (40.9%)
What are your program's/department's management approaches for patients with ALL							
Prophylaxis	57/195 (29.2%)	4/20 (20.0%)	27/70 (38.6%)	3/8 (37.5%)	12/54 (22.2%)	4/9 (44.4%)	6/22 (27.3%)
Diagnostic driven	68/195 (34.9%)	7/20 (35.0%)	24/70 (34.3%)	3/8 (37.5%)	18/54 (33.3%)	4/9 (44.4%)	5/22 (22.7%)
Empirical	70/195 (35.9%)	9/20 (45.0%)	19/70 (27.1%)	2/8 (25.0%)	24/54 (44.4%)	1/9 (11.1%)	11/22 (50.0%)
What are your program's/department's management approaches for fever in neutropenic patients?							
Diagnostic driven	67/263 (25.5%)	12/25 (48.0%)	24/99 (24.2%)	4/15 (26.7%)	12/69 (17.4%)	4/16 (25.0%)	6/25 (24.0%)
Empirical	196/263 (74.5%)	13/25 (52.0%)	75/99 (75.8%)	11/15 (73.3%)	57/69 (82.6%)	12/16 (75.0%)	19/25 (76.0%)
What are your program's/department's management approaches for ICU patients with invasive candidiasis or candidemia?							
Prophylaxis	16/261 (6.1%)	2/22 (9.1%)	9/99 (9.1%)	3/16 (18.8%)	1/70 (1.4%)	1/15 (6.7%)	0
Diagnostic driven	124/261 (47.5%)	8/22 (36.4%)	51/99 (51.5%)	3/16 (18.8%)	35/70 (50.0%)	9/15 (60.0%)	11/25 (44.0%)
Empirical	121/261 (46.3%)	12/22 (54.5%)	39/99 (39.4%)	10/16 (62.5%)	34/70 (48.6%)	5/15 (33.3%)	7/14 (50.0%)
Note. No. of respondents with "Not applicable to me", "I don't know" or "refer to ID" were excluded for analysis.							
Which guideline do you follow for managing fungal infections?							
Overall [N = 292]	China [n = 34]	India [n = 109]	Indonesia [n = 17]	Philippines [n = 74]	Singapore [n = 17]	Taiwan [n = 27]	Thailand [n = 14]
IDSA	227/292 (77.7%)	19/34 (55.9%)	81/109 (74.3%)	8/17 (47.1%)	65/74 (87.8%)	15/17 (88.2%)	26/27 (96.3%)
ESCMID	74/292 (25.3%)	7/34 (20.6%)	18/109 (16.5%)	5/17 (29.4%)	12/74 (16.2%)	4/17 (23.5%)	21/27 (77.8%)
Local country guidelines	76/292 (26.0%)	26/34 (76.5%)	11/109 (10.1%)	4/17 (23.5%)	13/74 (17.6%)	1/17 (5.9%)	19/27 (70.4%)
Institutional/unit guidelines	75/292 (25.7%)	6/34 (17.7%)	34/109 (31.2%)	8/17 (47.1%)	12/74 (16.2%)	5/17 (29.4%)	7/27 (25.9%)
Other	12/292 (4.1%)	1/34 (2.9%)	3/109 (2.8%)	1/17 (5.9%)	6/74 (8.1%)	1/17 (5.9%)	0
Which guideline do you follow for managing fungal infections?							
Overall [N = 292]	ID physicians [n = 151]		Non-ID physicians [n = 141]				
IDSA	227/292 (77.7%)		132/151 (87.4%)				
ESCMID	74/292 (25.3%)		59/151 (39.1%)				
Local country guidelines	76/292 (26.0%)		49/151 (32.5%)				
Institutional/unit guidelines	75/292 (25.7%)		21/151 (13.9%)				
Other	12/292 (4.1%)		2/151 (1.3%)				
Do you have an antifungal stewardship program in your hospital?							
Overall [N = 292]	China[n = 34]	India[n = 109]	Indonesia[n = 17]	Philippines[n = 74]	Singapore[n = 17]	Taiwan[n = 27]	Thailand[n = 14]
Yes	88/292 (30.1%)	13/34 (38.2%)	29/109 (26.6%)	2/17 (11.8%)	18/74 (24.3%)	2/17 (11.8%)	15/27 (55.6%)
No	204/292 (69.9%)	21/34 (61.8%)	80/109 (73.4%)	15/17 (88.2%)	56/74 (75.7%)	15/17 (88.2%)	9/14 (64.3%)

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ICU, intensive care unit; ID, infectious disease; IDSA, Infectious Diseases Society of America; MDS, myelodysplastic syndrome.

literature supports the value of ID consults (Lee et al., 2018; Burnham et al., 2018; Hamandi et al., 2014; Byl et al., 1999; Spec et al., 2016; Tang et al., 2017; Saunderson et al., 2015). Conditions shown to benefit from the involvement of an ID physician include staphylococcal bacteremia, transplant infections, multidrug-resistant infections and, most significantly, candidemia and cryptococcosis (Lee et al., 2018; Burnham et al., 2018; Hamandi et al., 2014). We do not know if the absence of ID services in the respondents' hospitals contributed to these figures – unfortunately, data on the presence or absence of an in-house ID team was not collected. Considering the published data on improvements achievable through the involvement of ID physicians, hospitals administering chemotherapy and performing transplants should be well served by an ID service. While admitting a bias, given our background as members of the ID community, we recommend referring patients who are suspected or confirmed to have IFD to an ID physician. Where ID physicians are in short supply, we suggest involving an ID physician in the development of an intra-hospital (or intra-departmental) guide on IFD management. Such a strategy

may also improve care, though it needs to be studied. Alternatively having an antifungal stewardship program should also be helpful, if the paucity of ID physicians prevents them from attending on individual cases. At the moment, antifungal stewardship programs are not common in the region (Table 3).

Many of the respondents followed the IDSA guidelines, perhaps because national guidelines on IFD are rare in this region. Despite this, the figure indicating the use of prophylaxis for AML/MDS was well below 100%. Perhaps drug accessibility and affordability prevented respondents from routinely implementing A1 recommendations, contributing to a discrepancy between the response to a general question and that to a specific question. Taiwanese respondents used IDSA and ESCMID guidelines, as well as national guidelines (Kung et al., 2018; Ko et al., 2018). These data are in accord with the availability of national guidelines. We also found that non-ID physicians tended to follow institutional guidelines, while ID physicians followed international or national guidelines. This likely reflects a knowledge gap, as non-ID physicians would resort to their hospital's website or to their intra-departmental

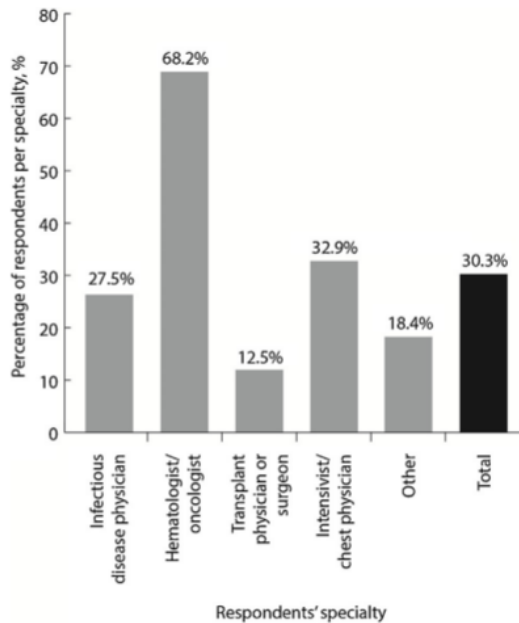


Figure 2. Respondents who used antifungal prophylaxis in patients with AML/MDS by specialty.

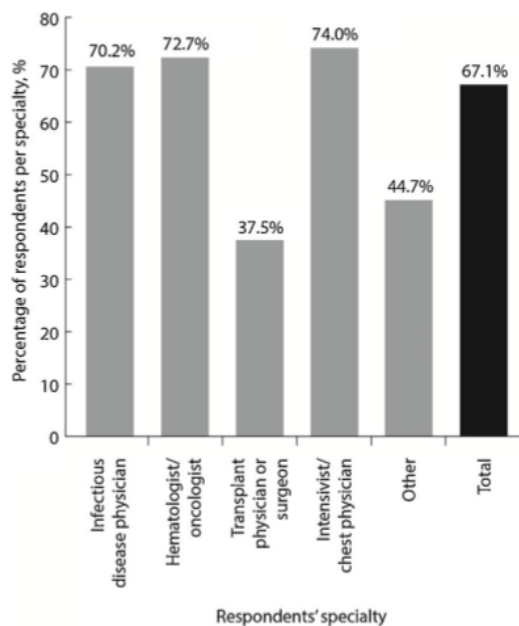


Figure 3. Respondents who used an empirical antifungal approach in patients with febrile neutropenia by specialty.

guide. It would appear that local guidelines have a role to play. Apart from guidelines, stewardship programs should also have an important role.

Differences in antifungal strategies were observed across countries and across specialties. For example, antifungal prophylaxis in the allo-HSCT and AML/MDS patient was more commonly employed in Singapore, Taiwan and India than in the other countries. Overall, empirical therapy was the main strategy for

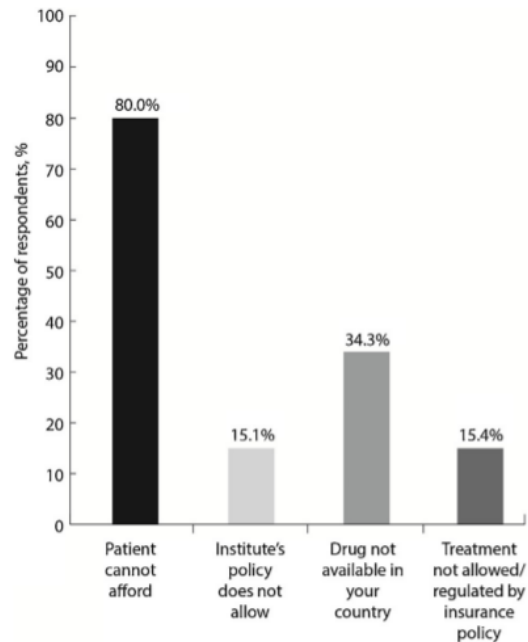


Figure 4. Factors preventing use of preferred antifungal agent; all respondents.

handling febrile neutropenia. Given the low numbers of hematologists/oncologists among the respondents, we suspect these answers reflect the respondents' general understanding of the management of these conditions in their hospital, likely arising from cross-referrals, grand rounds, and perhaps text messages during the survey. These findings also reflect the limitations in diagnostic modalities. In addition, the overall high proportions of "Not applicable" or "I don't know" responses for IFD management approach in patients with acute leukemia and allo-HSCT ($\geq 30\%$) versus those for ICU patients with invasive candidiasis ($< 5\%$) likely suggest that IFD management in patients with hematological malignancies and allo-HSCT constitute a niche specialty. Conceivably, dedicated personnel with special interest in the subject will help improve outcomes.

It is unfortunate, however, that the most common reasons for not using the antifungal drug of choice were the cost (80%) and non-availability of the drugs (34%). Cost was an impediment even in what might be considered the wealthier countries (Singapore, Taiwan), and likely reflects healthcare financing peculiarities. Indeed, Taiwanese respondents cited insurance limitations as the main reason (77.8%). Oddly, given that all antifungal agents are currently available in Taiwan, 25.9% of Taiwanese physicians indicated "Drug not available in your country" as a reason for not using their preferred antifungal agent. We hypothesize that physicians who have limited experience in managing IFD misclassified "drug not available in your institute" as "drug not available in your country".

The majority (70%) of 292 respondents agreed that country-specific training courses, improvement of laboratory diagnostic methods in hospitals and development of institute-based or country guidelines are top strategies to improve the management of IFDs. Few efforts have been carried out to fulfil these needs. The AFWG has conducted courses on medical mycology in Indonesia, Malaysia, the Philippines, Singapore, Taiwan, Thailand and Vietnam in the last 9 years (Asia Fungal Working Group, 2020a). Laboratory attachments sponsored by the AFWG have also been

Table 4
Country comparison of survey responses from physicians in 7 Asian countries: Recommendation.

	Overall [N = 291]	China [n = 34]	India [n = 108]	Indonesia [n = 17]	Philippines [n = 74]	Singapore [n = 17]	Taiwan [n = 27]	Thailand [n = 14]
How would you like to improve the management of fungal infections?								
Country-specific training courses	206/291 (70.8%)	26/24 (76.5%)	74/108 (68.5%)	11/17 (64.7%)	56/74 (75.7%)	11/17 (64.7%)	18/27 (66.7%)	10/14 (71.4%)
Asia-Pacific training courses conducted by the Asia Fungal Working group	172/291 (59.1%)	23/34 (67.7%)	54/108 (50.0%)	13/17 (76.5%)	46/74 (62.2%)	12/17 (70.6%)	18/27 (66.7%)	6/14 (42.9%)
Improvement of diagnostic tests in your hospital	219/291 (75.3%)	27/34 (79.4%)	71/108 (65.7%)	14/17 (82.4%)	62/74 (83.8%)	9/17 (52.9%)	25/27 (92.6%)	11/14 (78.6%)
Development of guideline for your institute/country	203/291 (69.8%)	22/34 (64.7%)	82/108 (75.9%)	12/17 (70.6%)	55/74 (74.3%)	9/17 (52.9%)	17/27 (63.0%)	6/14 (42.9%)
Improve drug availability in your country	132/291 (45.4%)	18/34 (52.9%)	37/108 (34.3%)	6/17 (35.3%)	46/74 (62.2%)	5/17 (29.4%)	12/17 (44.4%)	8/14 (57.1%)
Research	138/291 (47.4%)	14/34 (41.2%)	48/108 (44.4%)	11/17 (64.7%)	44/74 (59.5%)	3/17 (17.7%)	15/17 (55.6%)	3/14 (21.4%)
Other	16/291 (5.5%)	0	9/108 (8.3%)	1/17 (5.9%)	5/74 (6.8%)	0	1/17 (3.7%)	0

organized to enhance the skills of young microbiologists from less privileged areas (Asia Fungal Working Group, 2020b). However, there are still huge unmet needs – support from governments and international agencies is needed to fill these gaps.

The major limitation of this study is that we do not know if we reached out to all, or even the majority of, clinicians who manage IFDs in the countries we surveyed. Given the size of the populations of China and Indonesia, they appear under-represented. We did exhort, repeatedly, our team to reach out to their compatriots through their personal connections, as well as through their local societies. We also cannot be certain that all respondents understood all the questions perfectly, as differences in the command of English by the respondents may be anticipated.

Nevertheless, this first attempt presents an aggregate picture of the problems faced by clinicians managing IFDs in the countries we surveyed; the picture might be rosier or bleaker in individual institutions. Many of the findings are consistent with our anecdotal understanding of the situation in our countries. Hence, we achieved our aim of identifying the gaps. The AFWG will work towards improving mycology training in Asia, but funds are a perpetual problem.

Contributors

BHT, AC and YCC were responsible for the conception, design and coordination of the study and data analysis and interpretation. All authors contributed to data collection, analysis and data interpretation. BHT, MC and YCC wrote the main part of the paper. All authors drafted or revised the manuscript, and approved the final submitted manuscript.

Declaration of interests

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2020.01.007>.

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