JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Adherence to recommendations for the evaluation and management of fungal infections in a referral teaching hospital in Iran: A retrospective cross-sectional study

Haura Atashgar[1], Hossein Khalili[1,2], Mohammadreza Salehi[2,3], Mostafa Mohammadi[4]

[1] Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[2] Research Center for Antibiotic Stewardship and Antimicrobial Resistance, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Infectious Disease, Imam Khomeini Hospital Complex, Tehran University of Medical Science, Tehran, Iran
[4] Department of Intensive Care Unit, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Introduction: Early diagnosis and appropriate management of fungal infections are critical for reducing complications and mortality in hospitalized patients. Due to the lack of appropriate local management protocols as well as the unavailability and cost of advanced tests for diagnosis of fungal infections, the irrational use of antifungals is a concern in developing countries.

Objectives: This study was designed to evaluate diagnosis and management of fungal infections in hospitalized patients.

Methods: In a retrospective cross-sectional study, the use of parenteral antifungal medications among hospitalized patients was evaluated according to the prepared protocols adapted from the international guidelines.

Results: Among 151 patients, diagnostic approaches were appropriate and inappropriate in 90 and 61 patients respectively. Indications for antifungal drug administration were empiric therapy (80.1%) followed by targeted therapy (19.2%) and prophylaxis (0.7%). The indications were appropriate and inappropriate in 123 and 28 patients respectively. Selection of antifungals was appropriate in 117 patients, inappropriate in 16 patients, and was not assessable in other cases. The doses of antifungal medications were appropriate and inappropriate in 111 and 14 patients respectively. Among 151 patients, the duration of treatment was appropriate just in 33 cases. The techniques for antifungal administration were appropriate in 133 patients and inappropriate in 18 cases.

Conclusions: Due to limited access to diagnostic tests, most parenteral antifungal medications were administered as empiric therapy. The diagnostic workups, treatment monitoring, and follow-up were inadequate in most patients. Development of local diagnostic and management protocols for invasive fungal infections and considering a stewardship program for antifungal medications are essential for each medical center.

Key words: Antifungal; invasive fungal infection; utilization.

J Infect Dev Ctries 2023; 17(3):411-417. doi:10.3855/jidc.16828

(Received 12 May 2022 – Accepted 23 September 2022)

Introduction

Several fungi have the potential to cause widespread diseases in human subjects [1]. Although most fungal diseases can be managed simply, the treatment of invasive fungal infections (IFIs) is a critical challenge and these infections are responsible for approximately 1.5 million deaths a year [2]. In the recent decade, the concern towards IFIs has increased considerably as the susceptible populations are increasing [2-5]. These infections can be categorized as endemic and opportunistic mycosis. Invasive candidiasis, aspergillosis, and mucormycosis are the most common opportunistic fungal infections respectively [5] Solid organ transplantation, malignancy, and chemotherapy, immune-mediated disorders, widespread use of corticosteroids and immunosuppressant medications, renal replacement therapy, critically illnesses, widespread use of catheters and devices, and surgical interventions are known main associated factors for opportunistic fungal infections [1,2].

Several strategies including prophylaxis, empirical, pre-emptive, or targeted therapy are recommended for the management of IFIs. Polyenes, azoles, and echinocandins are the most commonly used antifungal agents in this era [3,5]. Unnecessary exposure, cost, adverse drug reactions, and increasing resistance may be caused by the irrational use of antifungal drugs [8].

The use of accurate and quick laboratory tests and techniques is important to consider these drugs in an appropriate way [3,5,9,10]. However, the lack of sensitive diagnostic tools in many settings may result in inappropriate and unnecessary antifungal drug administration. So, applying antifungal stewardship programs is essential to manage the use of antifungal agents [11,12].

Due to a lack of appropriate local management protocols as well as the unavailability and cost of advanced tests and techniques for the diagnosis of fungal infections, the irrational use of antifungals is a concern in developing countries. The aims of this study were to evaluate both the diagnosis and management of fungal infections in hospitalized patients.

Methods

Hospital setting

This study was conducted in Imam Khomeini Hospital Complex, Tehran, Iran. The hospital is a referral tertiary teaching center and is affiliated with Tehran University of Medical Sciences (TUMS).

Design and population

In a retrospective cross-sectional study (between March 2019 and December 2020), adult patients (≥ 18 years) who received any parenteral systemic antifungal drugs for at least 24 hours were included. Patients with incomplete medical records were excluded.

Data collection

Patients' demographic data, baseline diseases, medications, causes of hospital admission, duration of hospitalization, interventions during the hospital stay, immune-system status, associated factors for fungal infections, diagnostic approaches to detect fungal infections, use of antifungal medications (time, type, dose and duration), monitoring of antifungal therapy and follow-up were collected from patients' medical records and the hospital information system.

Protocol development

To evaluate diagnostic and treatment approaches for fungal infections, the study protocols were developed (Supplementary Figures 1-4). Protocols for diagnosis and management of invasive aspergillosis and candidiasis were adapted from the Infectious Diseases Society of America (IDSA) guidelines [13,14]. European Confederation of Medical Mycology (ECMM) guide was applied for mucormycosis [15]. Also, some articles have been used for developing the protocols [16-20]. The protocols were reviewed and finalized by two independent infectious diseases specialists and also two clinical pharmacists. Besides clinical findings and physical examinations, several molecular, biochemical, radiological, mycology, and histopathology studies and fungal smear, staining, and culture are recommended for diagnosis of fungal infections. Preferred antifungal regimens and alternatives are recommended in the international guidelines. Appropriate monitoring during the treatment course and end-of-treatment follow-up programs are crucial for the successful management of invasive fungal infections.

Data evaluation

Patients' medical charts review and data extraction were done by clinical pharmacists. If a patient received parenteral antifungals for more than one period, only the first episode was included. Patients' data have been reviewed in the scientific committee sections. The scientific committee consisted of two clinical pharmacists, two infectious diseases specialists, an intensivist, and a hospital pharmacist.

Definitions

Applied diagnostic tests (fungal smear, staining, culture, biomarkers, pathological and radiological findings), indications (prophylaxis, empiric or direct therapy), time form suggestion of fungal infection to starting drug (within 24 hours), selected antifungal (first choice and alternatives), dose (according to patient's weight, renal and liver function), techniques of preparation and administration of antifungal (vial reconstitution, dilution, peripheral or central line and rate of administration, incompatibility, premedication), monitoring (hemodynamic parameters, vital signs, renal and liver function assessments, electrolytes and other necessary laboratory tests, and therapeutic drug monitoring) and duration of therapy (considering the type of infection, assessment of the response to the therapy, follow-up tests, and imaging) were evaluated in the committee. These parameters were compared with the developed protocols and named as appropriate (if complied) and inappropriate (if not complied).

Parenteral broad-spectrum antibiotics for more than 10-14 days are considered long-term antibiotic therapy. Also, a hospital stay of more than 5 days is defined as long-term hospitalization. Long-term catheter is defined as any indwelling catheter for more than 14 days. 'Patient's immune system status was evaluated considering using immunosuppressive agents, history of organ or bone marrow transplant, or autoimmune

diseases. Neutropenia was defined as circulation neutrophils less than 1500 cells/μL.

Ethical approval

The Ethics Committee of Tehran University of Medical Sciences approved the study (ID: IR.TUMS.TIPS.REC.1398.185).

Statistical analysis

The quantitative variables have been expressed as mean ± standard deviation and qualitative variables as frequency (%). Correlation between antifungals' administration indexes and the patients' outcomes (length of hospital stay and mortality) have been evaluated by the Bivariate Pearson Correlation. Significant correlations have been expressed as OR (95% CI) according to the Binary Logistic Regression model. A p value < 0.05 was considered significant. Statistical Package for the Social Sciences (SPSS) software (version 25.0) was applied for data analysis.

Results

During the study, 151 patients received parenteral systemic antifungal medications. Mean ± SD of patients' age was 53.64 ± 18.32 years and most of them were male (52.35%). Regarding to the site of care, 62.3% of patients were admitted to Intensive Care Unit (ICU) and the rest were in the medical wards. The median length of hospitalization was approximately 33.5 days.

Table 1 shows patients' demographic, clinical characteristics, associated factors for fungal infections, and outcomes. Indwelling catheters, immunosuppression, sepsis, and long-term hospitalization were the most commonly associated factors with fungal infections respectively.

Diagnostic workup and follow-up

Fungal infections were diagnosed according to the clinical findings (signs and symptoms, physical examinations, and patients' baseline conditions) in 68.2% of patients. For 17.2% of patients, antifungal medications were considered because of the positive fungal culture of the biological samples. Radiological and clinical findings were the reasons for antifungal therapy in 4.6% and 4% of patients respectively.

The diagnostic approaches were appropriate and inappropriate in 59.6% and 40.4% of patients respectively. Considering follow-up programs, only 26.5% of patients had appropriate approaches and 58.9% and 14.6% of patients were inappropriate or inaccessible respectively.

Laboratory tests

Table 2 shows mycology test results and the origins of the proven fungal infections. *Candida* species almost always just recorded as *Candida albicans* or *none-albicans*.

Antifungal indications and time of administration

Indications for antifungal medications were empiric therapy (80.8%) followed by targeted therapy (18.5%)

Table1. Patients' demographic and clinical characteristics (n = 151).

Variable	N (%)
Age (year), (mean ± SD)	53.64 ± 18.32
Sex	
Female	72 (47.7)
Male	79 (52.3)
Length of hospitalization (day), (mean ± SD)	33.5 ± 24.28
Duration of hospitalization before fungal infection diagnosis (day), (mean ± SD)	13.18 ± 14.12
Immune system status	
Immunocompromised	93 (61.6)
Immunocompetent	58 (38.4)
Neutropenic patients	7 (4.6)
Antifungal administration targets	
Mucormycosis	25 (16)
Aspergillosis	4 (3)
Aspergillosis or Mucurmycosis	13 (9)
Candida spp.	109 (72)
Associated factors for invasive fungal infections	
Diabetes mellites	51 (33.8)
Cancer	42 (27.8)
Immunosuppression	93 (61.6)
Long-term catheter	99 (65)
Long-term antibiotic therapy	49 (32.5)
Long-term hospitalization	63 (41.7)
Surgery	44 (29.1)
Sepsis	68 (45)
Chemotherapy	10 (6.6)
Parenteral nutrition	7 (4.6)
Baseline diseases	
Diabetes mellitus	19 (12.6)
Cardiovascular	5 (3.3)
Neurologic disorders	3 (2)
Gastrointestinal disorders	32 (21.2)
Autoimmune diseases	1 (0.7)
Cancer	27 (17.9)
Covid-19	31 (20.5)
Others	34 (22.5)
Site of care	
Intensive Care Unit	94 (62.3)
Medical wards	57 (37.7)
Cause of ICU admission	
Medical	50 (33.1)
Surgical	31 (20.5)
Loss of consciousness	12 (7.9)
Need for vasopressor	1 (0.7)
Outcome	
Deceased	94 (62.3)
Discharged	57 (37.7)

and prophylaxis (0.7%). The reasons for empirical therapy were *Candida* score of more than 2.5, persistent fever for 2-3 days despite broad-spectrum antibiotic therapy, and clinical or radiological findings for mucormycosis, aspergillosis or esophageal candidiasis.

In 71.5% of patients, fungal infections were suspected according to the diagnostic measures whereas it was definite for 16.6% of patients. The diagnosis of fungal infection was unlikely in 11.9% of patients who received antifungal medications. Indications for antifungal therapy in 81.5% and 18.5% of patients were appropriate and inappropriate respectively (Table 3).

Regarding the starting time of antifungal therapy, it was on time in 59.6% of cases but was with delay in 28.5% of patients.

Selected drug and dose

Caspofungin was the most commonly used antifungal agent (51.7%) followed by liposomal (17.9%) and conventional formulations of amphotericin B (7.3%), fluconazole (12.9%) and voriconazole (1.3%). In 9.2% of cases, both liposomal and conventional formulations of amphotericin B were administered in one treatment course and were changed with each other based on availability in the hospital. In general, selected antifungal drugs were appropriate in 77.5% of patients, inappropriate in 10.6% of patients, and were not assessable in other cases.

Dose of antifungal medications were appropriate and inappropriate in 73.5% and 9.3% of patients respectively. Evaluation of other patients in this regard was impossible because the indications or selected drugs were inappropriate.

Duration of treatment, monitoring, and administration techniques

Duration of treatment was appropriate just in 21.9% of cases. It was inappropriate in 36.4% of the patients and was not assessable in 41.7% of individuals as they deceased during antifungal treatment or received antifungal therapy inappropriately.

Table 2. Finding of mycology tests.

Parameter	N (%)
Culture-positive samples	
Urine	29 (17.4)
Blood	18 (10.8)
Tracheal discharge	8 (4.8)
Central line catheter	4 (2.4)
General fluid	4 (2.4)
Other catheters	2 (1.2)
Smear-positive samples	6 (3.6)
Histopathology	7 (4.2)
Detected fungi	
Candida albicans	26 (15.6)
Candida none- albicans	34 920.4)
Mucormycosis	6 (3.6)
Aspergillus	7 (4.2)

Therapeutic drug monitoring (TDM) was not available and patients were only monitored for clinical response and adverse drug reactions.

Antifungals' administration techniques were appropriate in 88% of patients and inappropriate in 12% of cases.

Appropriateness of antifungals' administration indexes (except dosage) improved patients' survival but not the length of hospital stays (Table 4).

Discussion

In this study, according to the adapted protocols from the international guidelines and related articles, parenteral systemic antifungal utilization for the management of hospitalized patients with suspected or confirmed candidiasis, invasive aspergillosis, and mucormycosis was evaluated.

This study revealed that diagnostic workups for more than half of patients were not adequate. In some cases, especially in critically ill patients, early detection of patients who were at risk for invasive candidiasis was missed. Also, in most cases, on-time and appropriate biological samples did not send for laboratory evaluations. Access to molecular, biochemical and cultural tests was limited. Although there are several fungal biomarkers for early detection of fungal infections, galactomannan level (GML) was the only fungal biomarker that measured for only 13 patients

Table 3. Assessment of antifungal therapy.

Parameter	Appropriate	Inappropriate	Not assessable
Diagnostic workup	62 (41.1%)	89 (58.9%)	-
Patients' follow-up	40 (26.5%)	89 (58.9%)	22 (14.6%)
Indication	123 (81.5%)	28 (18.5%)	-
Time of administration	90 (59.6%)	43 (28.5%)	18 (11.9%)
Selected antifungal	117 (77.5%)	16 (10.6%)	18 (11.9%)
Dosage	107 (70.9%)	10 (6.6%)	34 (22.5%)
Duration of treatment	33 (21.9%)	55 (36.4%)	63 (41.7%)
Treatment monitoring	0	127 (84.1%)	24 (15.9%)
Administration technique	133 (88%)	18 (12%)	-

with suspected invasive aspergillosis. These limitations can lead to the irrational use of antifungal drugs in clinical practice. In a multicenter, two-times (first in June 2015 and the other in July 2017) point prevalence study (PPS) in Greek by Arvaniti *et al*, it has been shown that the absence of capacity to perform biological markers measurement led to an increase in the use of posaconazole as prophylaxis against *Candida spp.* and filamentous fungi infections [21].

Ultrasonography as the first choice and computed tomography (CT) scan as an alternative are the imaging techniques that are recommended in patients with possible candiduria to detect abscess formation, obstruction, or fungus ball presence [22]. These diagnostic approaches are never conducted in patients with possible candiduria. Also, esophagoscopy as a choice procedure in patients with possible esophageal candidiasis was never performed. Sometimes, for patients with possible mucormycosis, some imaging techniques such as a CT scan or Magnetic Resonance Imaging (MRI) were not considered [23].

Approximately only for one out of four patients, an appropriate follow-up program has been considered. Repeated fungal culture after 48 hours of starting treatment for proven candida infections, serial GML measurements to screen the treatment response of invasive aspergillosis, and serial appropriate imaging to monitor the treatment response of mucormycosis are from such recommended follow-up programs [13,14, 24].

Antifungal drugs were administered as empiric therapy in most cases and in more than 80% of occasions this decision was appropriate. In a study by Valerio *et al.*, performed at a tertiary teaching hospital in Madrid, Spain between December 2010 to January 2011, empiric therapy was the major reason for antifungal administrations followed by pre-emptive (20%) and targeted therapy (20%). The study also addressed that for 16% of cases antifungal therapy was unnecessary [25]. In an observational, cross-sectional study conducted in a Brazilian tertiary care hospital between January and December 2013, pre-emptive therapy was the most therapeutic strategy (50.9%) followed by targeted (19.7%) and empirical (17.5%) therapy, respectively [8]. The study also showed that 84.1% of indications were appropriate.[8] The results of the study by Arvaniti *et al*. indicated that empirical therapy was the common (30%) indication for antifungal prescriptions and the overall antifungal therapy assessment (indication, selected antifungal, or dosage) was inappropriate in 25% of patients [21].

In our evaluation, caspofungin was the most commonly administered antifungal medication followed by liposomal amphotericin B. Selected antifungal agents were inappropriate in 10.6% of patients. Caspofungin was often prescribed as empirical therapy for patients with possible candidemia and liposomal amphotericin B was administered mostly in patients with clinical or radiological findings of mucormycosis. The use of caspofungin for candiduria and fluconazole for candidemia as empirical therapy were the most cases of inappropriate antifungal agent selection.

In other investigations, including Valerio *et al.* [25], Reis *et al.* [8], and Arvaniti *et al.* [21], fluconazole was the most commonly administered antifungal but in Poulat *et al.* study caspofungin was first antifungal drug [26]. In this retrospective research which was performed at Haute-Pierre University Hospital, Strasbourg, France in 2012, 61% and 22% of antifungals were used as targeted and empiric therapy respectively. The overall assessment showed that both antifungal indication and selection were appropriate in 91% of cases [26].

The current study showed that in Imam Khomeini Hospital Complex, 73.5% of cases received appropriate antifungal dosage. Caspofungin dose was almost always appropriate according to the protocol but patients did not receive an adequate dose of fluconazole, liposomal amphotericin B, and conventional amphotericin B. In a study by Reis *et al.*, 67.8% of antifungal drugs dosage were appropriate. Route of administration, missed calculating dose based on patients' age and weight, lack of dose adjustment, and applied different dosing range were main subjects for inappropriate antifungals dosing [8]. According to

Table 4. Effects of antifungals administration indexes on patients' outcomes.

Index	Length of hospitalization (*p* value)	Mortality OR (95% CI)
Appropriateness of diagnostic workups	0.25	0.44 (0.22-0.88)
Appropriateness of indication	0.32	0.29 (0.10-0.83)
Appropriateness of time of administration	0.95	0.32 (0.17-0.60)
Appropriateness of selection	0.76	0.65 (0.42-0.98)
Appropriateness of dosage	0.10	0.67 (*p* value)
Appropriateness of duration	0.14	0.32 (0.22-0.47)
Appropriateness of administration techniques	0.55	0.23 (0.07-0.83)

Poulat *et al.*, 89% of antifungal drugs were administered with appropriate dosage [26].

Antifungal agents were started with considerable delay in 28.5% of cases. This may be due to insufficient workups and lack of diagnostic tools.

Therapeutic drug monitoring (TDM) of antifungals was not applied. However, TDM is recommended for selected antifungals (itraconazole, voriconazole, and posaconazole) to optimize the treatment regimens [27]. Inadequate antifungal blood concentrations can lead to poor clinical outcomes [28]. If it is available, antifungal TDM may be considered for selected antifungal medications and also for patients with probable changes in the pharmacokinetics parameters [11]. Anyway, TDM is expected at least for voriconazole, a drug with variable pharmacokinetic behavior.

Invasive fungal infections can cause considerable mortality especially in immunocompromised and critically ill patients [10]. Considering the inappropriate use of antifungal medications and current trends in acquired antifungal resistance, applying stewardship programs are essential [29]. According to IDSA suggestion for Antifungal Stewardship (AFS) programs, clinical pharmacists, clinical microbiologists and infectious disease specialists are the main members of AFS team [29]. Unfortunately, this is an important gap in our hospital.

Our study suffered from some major limitations including being retrospective with a small sample size, lack of some information in the Hospital Information System (HIS) database, defects in patients' medical records, antifungal availability, and in a few cases unclear reasons for antifungal therapy. Also, oral antifungals were not evaluated.

Conclusions

There was no local protocol for the diagnosis and treatment of invasive fungal infections in this center. The lack of diagnostic approaches and laboratory tests were the main alarming findings of this study. Indications of antifungal medications were empiric in most cases. Antifungal agents were selected appropriately for most cases with suspected or confirmed infections. There was no knowledge or attitude regarding therapeutic drug monitoring for antifungal medications. The establishment of antifungal stewardship programs in the hospital is essential.

Acknowledgements

We would like to thank the nurses and other staff of Imam Khomeini Hospital Complex for their kind support. No grant was received regarding this work.

Authors' Contributions

Haura Atashgar: Data gathering; Hossein Khalili: Study design, data interpretation, final revising of the manuscript; Mohammadreza Salehi: Patients' assessment; Mostafa Mohammadi: Patients' assessment

References

1. Tudela JLR, Denning DW (2017) Recovery from serious fungal infections should be realisable for everyone. Lancet Infect Dis 11: 1111-1113.
2. Armstrong-James D, Brown GD, Netea MG, Zelante T, Gresnigt MS, van de Veerdonk FL, Levitz SM (2017) Immunotherapeutic approaches to treatment of fungal diseases. Lancet Infect Dis 12: e393-e402.
3. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A (2017) The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis 12: e383-e392.
4. Casadevall A (2018) Fungal Diseases in the 21st Century: The Near and Far Horizons. Pathog Immun 2: 183-196.
5. Hoenigl M, Salmanton-García J, Walsh TJ, Nucci M, Neoh CF, Jenks JD, Lackner M, Sprute R, Al-Hatmi AMS, Bassetti M, Carlesse F, Freiberger T, Koehler P, Lehrnbecher T, Kumar A, Prattes J, Richardson M, Revankar S, Slavin MA, Stemler J, Spiess B, Taj-Aldeen SJ, Warris A, Woo PCY, Young JH, Albus K, Arenz D, Arsic-Arsenijevic V, Bouchara JP, Chinniah TR, Chowdhary A, de Hoog GS, Dimopoulos G, Duarte RF, Hamal P, Meis JF, Mfinanga S, Queiroz-Telles F, Patterson TF, Rahav G, Rogers TR, Rotstein C, Wahyuningsih R, Seidel D, Cornely OA (2021) Global guideline for the diagnosis and management of rare mould infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and the American Society for Microbiology. Lancet Infect Dis 8: e246-e257.
6. Houšť J, Spížek J, Havlíček V (2020) Antifungal Drugs. Metabolites 3: 106.
7. Rudramurthy SM, Paul RA, Chakrabarti A, Mouton JW, Meis JF (2019) Invasive Aspergillosis by *Aspergillus flavus*: Epidemiology, Diagnosis, Antifungal Resistance, and Management. J Fungi (Basel) 3: 55.
8. de Souza MC, Dos Santos AG, Reis AM (2016) Drug utilization study of systemic antifungal agents in a Brazilian tertiary care hospital. Int J Clin Pharm 6: 1398-1406.
9. Cole DC, Govender NP, Chakrabarti A, Sacarlal J, Denning DW (2017) Improvement of fungal disease identification and management: combined health systems and public health approaches. Lancet Infect Dis 12: e412-e419.
10. Johnson MD, Lewis RE, Dodds Ashley ES, Ostrosky-Zeichner L, Zaoutis T, Thompson GR, Andes DR, Walsh TJ, Pappas PG, Cornely OA, Perfect JR, Kontoyiannis DP (2020) Core recommendations for antifungal stewardship: a statement of the mycoses study group education and research consortium. J Infect Dis Suppl 3: S175-S198.
11. Hamdy RF, Zaoutis TE, Seo SK (2017) Antifungal stewardship considerations for adults and pediatrics. Virulence 6: 658-672.

12. Vazin A, Davarpanah MA, Ghalesoltani S (2015) Antifungal agent utilization evaluation in hospitalized neutropenic cancer patients at a large teaching hospital. Drug Healthc Patient Saf 7: 97-102.
13. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE (2016) Practice Guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 4: e1-e60.
14. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD (2016) Clinical practice guideline for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 4: e1-50.
15. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, Hoenigl M, Jensen HE, Lagrou K, Lewis RE, Mellinghoff SC, Mer M, Pana ZD, Seidel D, Sheppard DC, Wahba R, Akova M, Alanio A, Al-Hatmi AMS, Arikan-Akdagli S, Badali H, Ben-Ami R, Bonifaz A, Bretagne S, Castagnola E, Chayakulkeeree M, Colombo AL, Corzo-León DE, Drgona L, Groll AH, Guinea J, Heussel CP, Ibrahim AS, Kanj SS, Klimko N, Lackner M, Lamoth F, Lanternier F, Lass-Floerl C, Lee DG, Lehrnbecher T, Lmimouni BE, Mares M, Maschmeyer G, Meis JF, Meletiadis J, Morrissey CO, Nucci M, Oladele R, Pagano L, Pasqualotto A, Patel A, Racil Z, Richardson M, Roilides E, Ruhnke M, Seyedmousavi S, Sidharthan N, Singh N, Sinko J, Skiada A, Slavin M, Soman R, Spellberg B, Steinbach W, Tan BH, Ullmann AJ, Vehreschild JJ, Vehreschild MJGT, Walsh TJ, White PL, Wiederhold NP, Zaoutis T, Chakrabarti A, Mucormycosis ECMM MSG Global Guideline Writing Group (2019) Global guideline for the diagnosis and management of mucormycosis: an initiative of the European confederation of medical mycology in cooperation with the mycoses study group education and research consortium. Lancet Infect Dis 12: e405-e421.
16. Elhoufi A, Ahmadi A, Asnaashari AM, Davarpanah MA, Bidgoli BF, Moghaddam OM, Torabi-Nami M, Abbasi S, El-Sobky M, Ghaziani A, Jarrahzadeh MH, Shahrami R, Shirazian F, Soltani F, Yazdinejad H, Zand F (2014) Invasive candidiasis in critical care setting, updated recommendations from "invasive fungal infections-clinical forum", Iran. World J Crit Care Med 4: 102-12.
17. Ahmadi A, Ardehali SH, Beigmohammadi MT, Hajiabdolbaghi M, Hashemian SM, Kouchek M, Majidpour A, Mokhtari M, Moghaddam OM, Najafi A, Nejat R, Niakan M, Lotfi AH, Amirsavadkouhi A, Shirazian F, Tabarsi P, Taher MT, Torabi-Nami M (2014) Invasive candidiasis in intensive care unit; consensus statement from an Iranian panel of experts, July 2013. JRSM Open 3: 2042533313517689.
18. Dimopoulos G, Antonopoulou A, Armaganidis A, Vincent JL (2013) How to select an antifungal agent in critically ill patients. J Crit Care 5: 717-27.
19. Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, Singh R, Shastri P, Umabala P, Sardana R, Kindo A, Capoor MR, Mohan S, Muthu V, Agarwal R, Chakrabarti A. (2020) A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect 7: 944.e9-944.e15.
20. Sipsas NV, Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP (2018) Therapy of mucormycosis. J Fungi (Basel) 3: 90.
21. Arvaniti K, Perdikouri EI, Samonis G, Kofteridis DP (2020) Hospital-wide antifungal prescription in Greek hospitals: a multicenter repeated point-prevalence study. Eur J Clin Microbiol Infect Dis 2: 243-248.
22. Odabasi Z, Mert A (2020) Candida urinary tract infections in adults. World J Urol 11: 2699-2707.
23. Mohamed AA, Lu XL, Mounmin FA (2019) Diagnosis and treatment of esophageal candidiasis: current updates. Can J Gastroenterol Hepatol 20: 3585136.
24. Alexander BD, Lamoth F, Heussel CP, Prokop CS, Desai SR, Morrissey CO, Baddley JW (2021) Guidance on imaging for invasive pulmonary aspergillosis and mucormycosis: from the imaging working group for the revision and update of the consensus definitions of fungal disease from the EORTC/MSGERC. Clin Infect Dis Suppl 2: S79-S88.
25. Valerio M, Rodriguez-Gonzalez CG, Muñoz P, Caliz B, Sanjurjo M, Bouza E, COMIC Study Group (Collaborative Group on Mycoses) (2014) Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed. J Antimicrob Chemother 7: 1993-9.
26. Poulat C, Nivoix Y, Launoy A, Lutun P, Bachellier P, Rohr S, Woehl ML, Levêque D, Bru V, Herbrecht R, Gourieux B (2017) Assessment of high-priced systemic antifungal prescriptions. Med Mal Infect 6: 382-388.
27. John J, Loo A, Mazur S, Walsh TJ (2019) Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients. Expert Opin Drug Metab Toxicol 11: 881-895.
28. Vena A, Muñoz P, Mateos M, Guinea J, Galar A, Pea F, Alvarez-Uria A, Escribano P, Bouza E (2020) Therapeutic drug monitoring of antifungal drugs: another tool to improve patient outcome? Infect Dis Ther 1: 137-149.
29. Hart E, Nguyen M, Allen M, Clark CM, Jacobs DM (2019) A systematic review of the impact of antifungal stewardship interventions in the United States. Ann Clin Microbiol Antimicrob 1: 24.

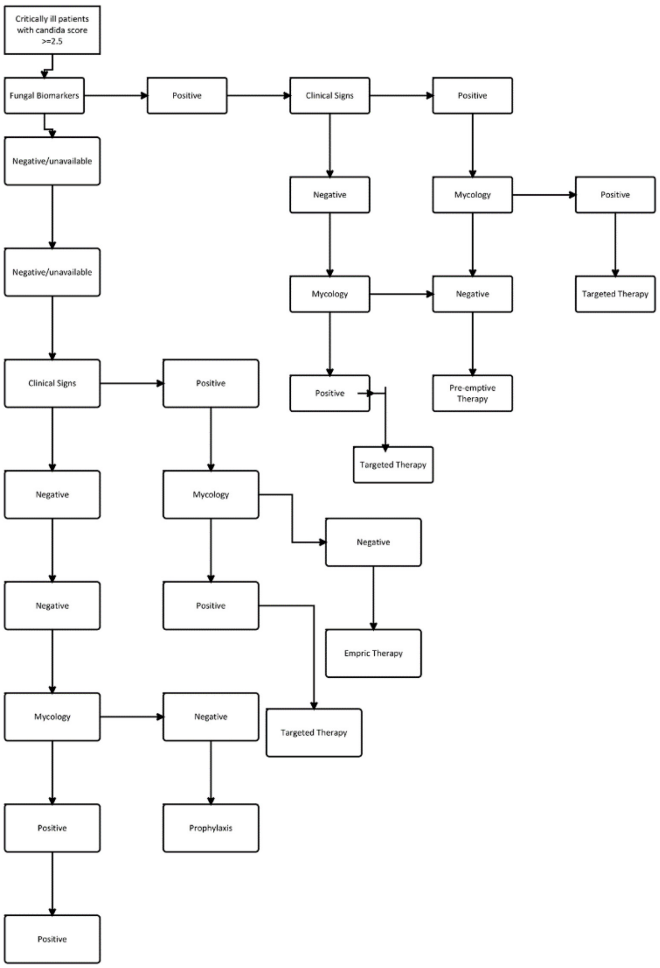
Corresponding author

Hossein Khalili
Department of Clinical Pharmacy,
School of Pharmacy
Tehran University of Medical Sciences,
Tehran, Iran -1417614411
P.O. Box: 14155/6451
Tel/Fax: +98-21-66954709
E-mail: khalilih@sina.tums.ac.ir

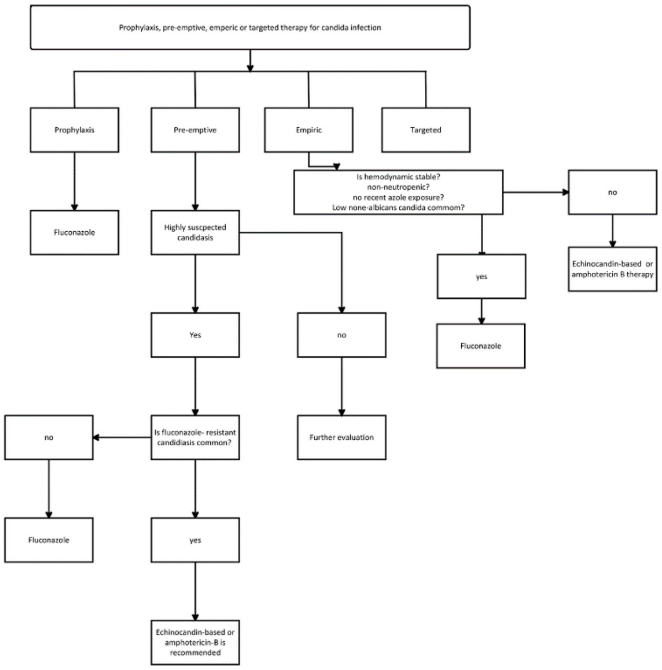
Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

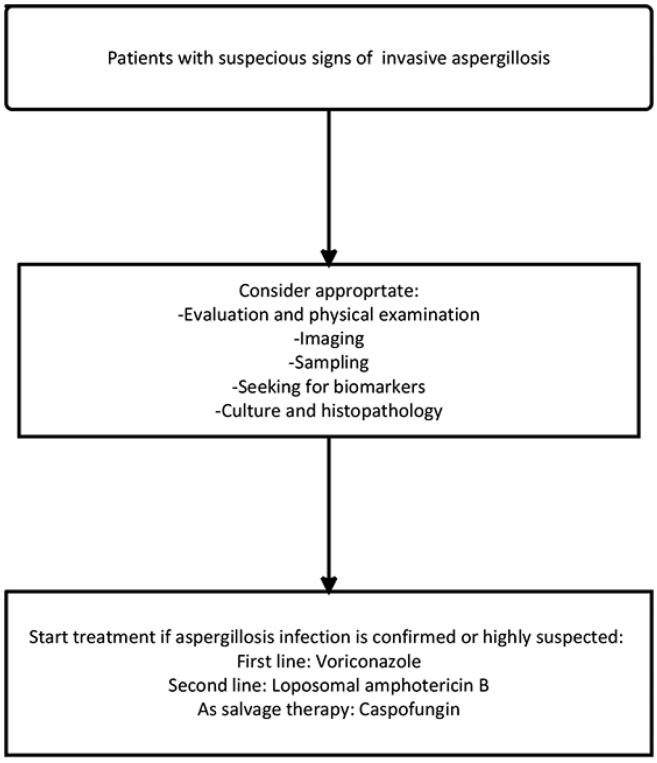
Supplementary Figure 1. Approach for diagnosis of candidiasis.



Supplementary Figure 2. Approach for treatment of candidiasis.



Supplementary Figure 3. Approach for diagnosis and treatment of aspergillosis.



Supplementary Figure 4. Approach for diagnosis and treatment of mucormycosis.