Review Article

Treatment of Invasive Fungal Infection: Recommendations from Scientific Leaders' Meeting on November 3rd, 2011 Tehran – Iran

Masoud Mardani [1] ,Payam Tabarsi [2] , Davood Yadegarinia [1], Mahshid Talebi Taher [3], Narges Najafi[4], Mahboobeh Hajabdolbaghi[5], Mehrnaz Rasooli Nejad [6],Parisa Badiei1, Alireza Janbakhsh [7], Hassan Salehi [8], Farzin Khorvash [9], Kouros Aghazadeh [10], Davood Mansouri [11], Najmeh Namazi[1],Monireh Kamali[1]

Abstract

There are many published international recommendations and guidelines for the management of Invasive Fungal Infections (IFIs). It is very important to develop Iranian recommendations to implement those guidelines in a daily routine practice in Iran considering the local specifications.
This was the objective of this meeting, which was held on November 3rd, 2011 in Tehran. 17 Iranian scientific leaders met and reviewed all the available published International Guidelines for management of IFIs in different groups of patients. This was followed by an open discussion to develop local recommendations for appropriate implementation of International Guidelines using the available treatments in Iran.
This review shows the outcome of this meeting. We believe that, putting these recommendations into practice may lead to better results of the management of cases with IFIs.

Introduction

The incidence of Invasive fungal infections is increasing. IFIs remain a major cause of morbidity and mortality among immune-compromised patients. And Candida species are an increasing cause of sepsis among non-neutropenic patients receiving intensive care.
Aadvances in diagnostic modalities have yield in earlier diagnosis of IFIS. Also clinical prediction rules have been developed to identify patients in ICU who are at high risk of Candidiasis. On the other hand new antifungal agents have improved the outcome of treatment.
This review is the result of experts' meeting which was held to develop Iranian Guidelines for treatment of invasive fungal infections. Guidelines have focused on three major groups: 1) Neutropenic patients (including Hematopoietic Stem Cell Trans plantation)
2) Solid Organ Transplant (SOT) recipients.
3) Intensive Care Unit (ICU) patients.
In each groups, two major topics are addressed:
A) Prophylaxis
B) Treatment

1) Neutropenic patients

A1: Prophylaxis against candida infection:

It is recommended in allogeneic hematopoietic stem cell transplant (HSCT) recipients or those undergoing intensive remission-induction or salvage induction chemotherapy for acute Leukemia.
For this purpose oral fluconazol (400 mg/ daily) is drug of choice. Other azoles such as itraconazole, voriconazole and posaconazole are alternative.
caspofungin may be used if azoles are contra indicated.

1A2: Prophylaxis against invasive Aspergillus infection:

When prophylaxis must be directed against aspergillosis?
-Prior invasive aspergillosis
-Anticipated prolonged neutropenic periods of at least 2 weeks.
- Prolonged period of neutropenia immediately prior to HSCT
- Induction phase for Acute Myeloid Leukemia (AML)
- Induction phase for Myelodysplastic Syndrome (MDS)

1.Infectious Diseases and Tropical Medicine Research Center ,Shahid Beheshti University of Medical Sciences ,Tehran ,Iran
2. Clinical TB and Epidemiology Research Center ,Shahid Beheshti University of Medical Sciences ,Tehran,Iran
3. Infectious Diseases Department ,Tehran University of Medical Sciences ,Tehran ,Iran
4. Assistant professor of Infectious Diseases ,Mazandaran University of Medical Sciences .Sari,Iran
5. Iranian Research Center of HIV and AIDS ,Tehran ,Iran
6. Imam Khomeini Hospital ,Tehran University of Medical Sciences ,Tehran ,Iran
7. Imam Reza Hospital Infectious Diseases Department, Kermanshah University of Medical Sciences ,Kermanshah ,Iran
8. Isfahan University of Medical Sciences ,Isfahan ,Iran
9. Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Science, Isfahan, Iran
10.Shahid Behshti University of Medical Sciences ,Tehran,Iran
11. Division of Infectious Diseases and Clinical Immunology, National Research Institute & Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Corresponding Author :Payam Tabarsi Clinical TB and Epidemiology Research Center ,Shahid Beheshti University of Medical Sciences ,Tehran,Iran
Email:payam Tabarsi@yahoo.com Tel:+989123307289
Received: 12 November 2011, Accepted: 19 December 2011

For this purpose Posaconazole is the only FDA Approved drug. But, Itraconazole and Voriconazole may be also be used.

1-A3: Duration:

For acute leukemia, prophylaxis must be continued till myeloid reconstitution. For HSCT recipients, prophylaxis must be continued for at least 75 days after transplantation or till cessation of immunosuppressive therapy.

1A4: Antifungal prophylaxis is not recommended for: patients ,in whom the anticipated duration neutropenia is less than 7 days.

1-B: Treatment of IFIs in neutropenic patients:

Two approaches are recommended:

1) Empirical approach: Antifungal should start for high risk patients with persistent fever after 4-7 days with antibiotics, and duration of neutropenia is expected to be >7 days. Investigations for IFIs should start with antifungal. But for all patients, antifungal with anti-mold coverage will be initiated; Caspofungin or L Amph B. Voriconazole is alternative. For patients receiving Anti-mold prophylaxis, switching to an IV form of anti-mold agent within a different class of antifungal is recommended.

2) Pre-emptive approach: is acceptable alternative approach for patients with unexplained fever (persistent fever for more than 4-7 days despite antibiotic) but clinically stable. CT-Scan of chest and Para nasal sinuses serial serum galactomannan test should be performed. If patient has a sign of IFI, anti-fungal with anti-mold activity should be initiated. For patients receiving Anti-mold prophylaxis, switching to an IV form of anti-mold agent within a different class of antifungal is recommended.

2) Solid Organ Transplant Recipients

2-A: Prophylaxis of fungal infections in solid organ transplant recipients:

2-A-1) Liver:

In the presence of one of these risk factors prophylaxis should be considered:

- Re-transplantation
- Renal failure
- Reoperation involving thoracic or abdominal cavity

For prophylaxis, lipid formulation of amphotericin or fluconazol is recommended. Echinocandins are alternative.

Prophylaxis must be continued for 4 weeks after transplantation.

2-A-2: Lung:

For all lung transplant recipients, prophylaxis with anti-mold drug is recommended. For this purpose inhaled amphotericin B, Itraconazole 200 mg BID or voriconazole 200 mg BID is recommended. Prophylaxis must be continued 4 months or longer.

2-A-3: Heart:

Patients who have one of these risk factors must receive anti-mold prophylaxis:

- Isolation of Aspergillus species in respiratory tract cultures
- Re-operation
- CMV disease
- Post transplant hemodialysis
- Existence of an episode of IA 2 months before or after heart transplant.

For this purpose Itraconazole 200 mg BID or Voriconazole 200 mg BID may be prescribed. Duration of prophylaxis is 50-150 days.

2-B: treatment of IFIs in Solid Organ Transplant Recipients:

Empirical Treatment of IFIs:

The possible criteria to begin empirical treatment for suspected invasive candidiasis in SOT recipients are as follows: (1) Persistent fever (_38°C) despite broad spectrum antibacterial therapy for _96 hours. and (2) no other known cause of fever. plus (3) Candida colonization for the same Candida species from at least 2 noncontiguous (including nonsterile) sites and/or (4) the presence of
specific risk factors and/or, (5) clinical-radiological suspicion of IC and/or detection of _-D-glucan in serum.

Suspect Candida:

- Fluconazole: in clinically stable patients with no prior exposure to azoles.
- Echinocandins in critically ill patient with previous exposure to azoles.
- L Amph B is an alternative.

Suspect Aspergillus:

- Voriconazole: for all patients with invasive Aspergillosis whatever the site of infection.
- L Amph B is an alternative
- Caspofungin: alternative and salvage therapy
- Posaconazole: alternative and salvage therapy

Treatment of established IFIs:

Consider the same treatment as empirical treatment for Candida and Aspergillus.

For Zygomycetes:

- Multiple debridements
- L Amph. high dose

Or

- Amph B
- Posaconazole: is step-down from L Amph B or salvage therapy.

3) IFIs in ICU Patients

3-A: Prophylaxis against IFIs in ICU:

Following patients must be considered for antifungal prophylaxis in ICU:

1) ICU patients with recurrent GI perforation or anastomotic Leakage.(IV fluconazol 400 mg once daily)

2) Patients admitted to a tertiary referral center ICU (surgical or medical) with a baseline risk for candidemia of 10% or greater if there is an anticipated of stay more than 3 days .(oral fluconazol 400 mg daily)

3-B: treatment of IFI in ICU

Diagnosis of IFIs in ICU patients is a challenging issue. Invasive Candidiasis is the main cause of IFIs in those cases. There are some scoring systems such as Candida score. Characterized by high specificity but a low sensitivity., These systems allow identification of only a

small proportion of ICU patients who might develop candidiasis.

Early initiation of antifungal therapy may reduce morbidity, mortality, and length of stay in critically ill patients, however the widespread use of these agents must be balanced against the risk of toxicity, costs, and the emergence of resistance.

Empirical antifungal therapy is recommended:

3-B-1 In critically ill patients or previous exposure to azoles:

Conclusion

Reviewing these recommendations, we considered the local specifications of Iran, and the available antifungal drugs in the Iranian market.

That's why; applying them in clinical practice is believed to improve the management of those patients in terms of decreasing mortality and morbidity especially for at risk patients. On the other hand, it may have a positive effect on decreasing hospitalization rate and duration of admission, which may have cost-effectiveness benefit.

It's recommended to update these recommendations periodically based on the results of applying the current ones, the future update of international guidelines and the availability of newer antifungal therapeutic options.

Table 1. ECIL-3 recommendations[a] on antifungal prophylaxis in leukaemic and haematopoietic stem cell transplant patients, for empirical therapy of febrile neutropenia and for first-line and salvage-directed treatment of invasive aspergillosis[1,20,21]

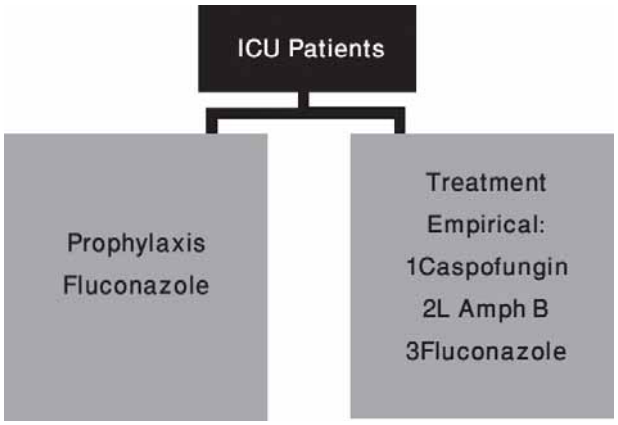
	Prophylaxis				Directed treatment of invasive aspergillosis	
Drug	allogeneic HSCT: neutropenic phase	allogeneic HSCT: GVHD phase	induction chemotherapy of acute leukaemia	Empirical therapy	first line	salvage
Amphotericin B deoxycholate	CI	CI	CI	efficacy BI, safety DI	DI	—
Liposomal amphotericin B	BII (aerosolized plus fluconazole)	—	BI (aerosolized plus fluconazole)	efficacy AI, safety AI	BI	BIII
ABCD	—	—	—	efficacy BI, safety BI	DI	—
ABLC	—	—	—	efficacy BI, safety BI	BII	BIII
Itraconazole	BI	BI	CI	efficacy BI, safety BI	CIII	CIII
Posaconazole	—	AI	AI	—	—	BII
Voriconazole	Provisional AI	Provisional AI	—	efficacy BI, safety BI	AI	BII
Caspofungin	—	—	—	efficacy AI, safety AI	CII	BII
Mcafungin	CI	—	—	efficacy BII, safety BII	—	—

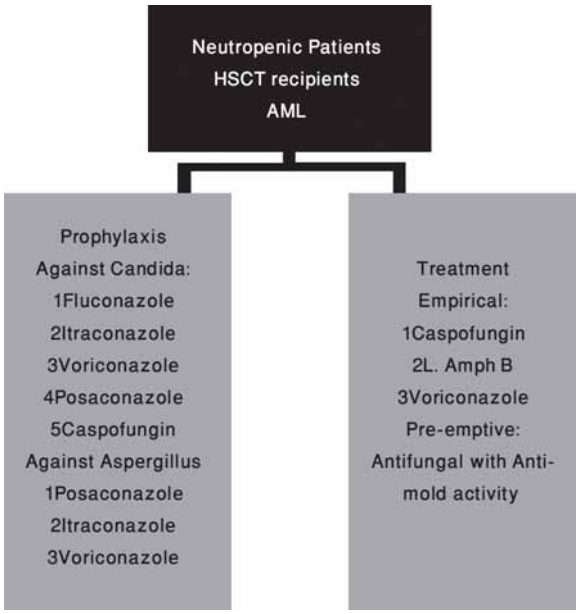
HSCT, haematopoietic stem cell transplantation; GVHD, graft versus host disease; ABLC, amphotericin B lipid complex; ABCD, amphotericin B lipid dispersion.
[a]Evidence was graded using the following criteria: I, evidence from at least one well-executed randomized trial; II, evidence from at least one well-designed clinical trial without randomization, cohort or case-controlled analytical studies (preferably from more than one centre), multiple time series studies, or dramatic results from uncontrolled experiments; III, evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports from expert committees. The following recommendation levels were used: A, strong evidence for efficacy and substantial clinical benefit; B, strong or moderate evidence for efficacy, but only limited clinical benefit; C, Insufficient evidence for efficacy, or efficacy does not outweigh possible adverse consequences (e.g. drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches; D, moderate evidence against efficacy or for adverse outcome—generally not recommended; E, strong evidence against efficacy or of adverse outcome—never recommended.

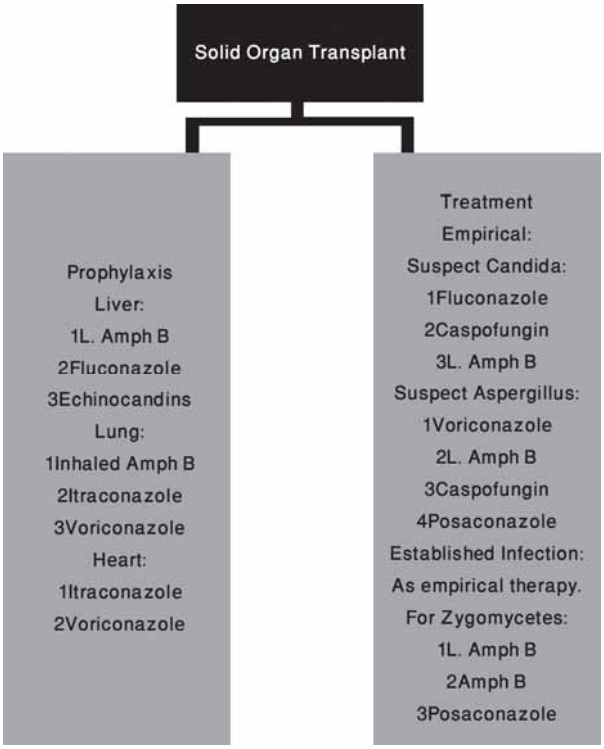
Table 3 ECIL 3 guidelines on empirical antifungal treatment in neutropenic patients with persistent or relapsing fever (the updated items are reported in bold italic)

Antifungal agent	*Daily dose*	*Level of recommendation*	*CDC grading Level of evidence for*	
			Efficacy	*Safety*
Liposomal ampho B	3 mg/kg	A[a]	I	I
Caspofungin	50 mg	A[a,b]	I	I
ABCD	4 mg/kg	B[c]	I	I
ABLC	5 mg/kg	B[c]	I	I
Itraconazole	200 mg i.v.	B[b,a]	I	I
Voriconazole	2 × 3 mg/kg i.v.	B[b,d,a]	I	I
Micafungin	***100 mg***	***B***	***II***	***II***
Ampho B deoxycholate	0.5–1 mg/kg	B[c]/D[f]	I	I
Fluconazole	400 mg i.v.	C[b,a,g]	I	I

Abbreviations: ABCD = amphotericin B colloidal dispersion; ABCL = amphotericin B lipid complex; ECIL = European Conference on Infections in Leukemia; FDA, Food and Drug Administration; HSCT = hematopoietic stem cell transplant.







References

1-Bow EJ, Evans G, fuller J et al, Canadian clinical practice guidelines for invasive candidiasis in adult. can infect dis med microbial 2010;21(4):e122-e150

2-Pagano L, Lumb J. update on invasive fungal disease. Future microbiol. 2011 6(9): 985-989.

3-Freifeld AG,bow EJ, sepkowitz LKA A, et al. clinical practice guideline for the use antimicrobial agents in neutropenic patients with cancer: 2010 update by the infection disease society of America.CID 2011;52(4):e56-e93

4-Pappas PE, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the infectious disease society of America. CID, 2009;48:503-35.

5-Walsh TJ, Anassie EJ, Denning DW, et al. treatment of Aspergillosis: clinical practice guidelines of the infectious diseases society of America. CID 2008: 46:327-60.

6-Grossi PA. Dalla Gaspenina D, Barchies F, et al, Italian guidelines for diagnosis, prevention and treatment of invasive frugal infection in solid organ transplant recipients. Transplant proceed 2011.43:2463-2471.

7-Ruiz –camps I, Aguado JM, Almirante B, et al. Guidelines for the prevention of invasive mould disease caused by filamentous fungi by the Spanish society of infectious diseases and clinical microbiology. Clin. microbial