Böbrek Nakledilmiş Hastalarda Fungal Enfeksiyonların Tedavi ve Profilaksisi

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Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

11.01.2026

Sunumun Amacı

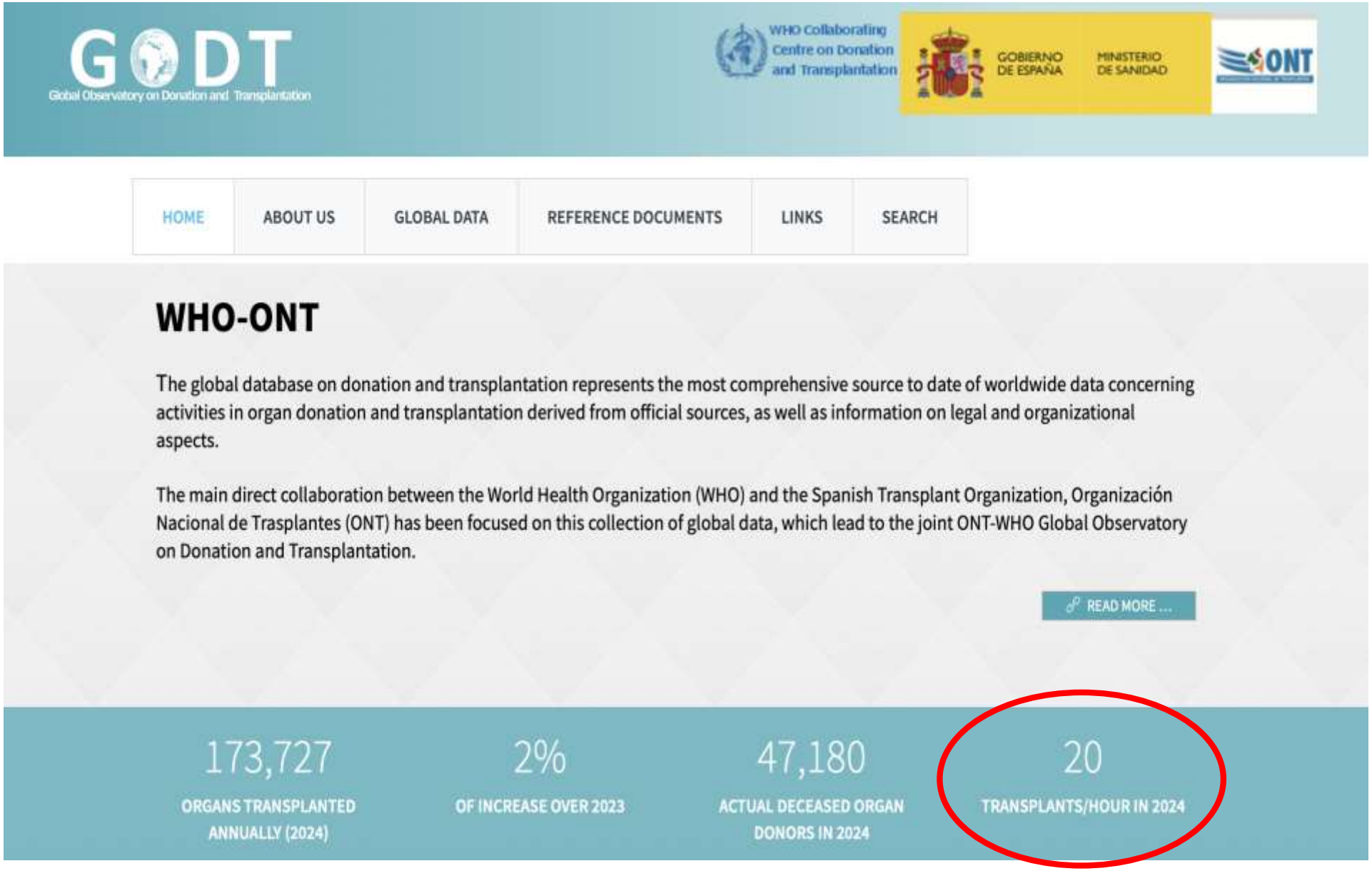
- Solid organ nakli alıcılarında invaziv fungal infeksiyonların (İFİ) önemini vurgulamak
- Risk temelli **profilaksi stratejilerini** özetlemek
- Kanıtlanmış enfeksiyonlarda **tedavi yaklaşımlarını** tartışmak
- Güncel rehberler ışığında **klinik pratik önerileri** sunmak

Neden önemli?

- SOT alıcılarında invaziv fungal infeksiyonlar (İFİ) yüksek mortalite ve greft kaybı ile ilişkilidir
- **Tanı gecikmesi sık;** antibakteriyel tedaviye yanıtsızlık “fungal” düşünmeyi zorunlu kılar…
- Erken tanı ve uygun antifungal strateji → **yaşam kurtarıcı**

Epidemiyoloji

- Enfeksiyon riski en yüksek dönem: **ilk 3 ay**
- Geç dönem:
  - Kronik rejeksiyon
  - Uzamış immünsüpresyon
- Etken dağılımı **nakledilen organa göre değişir**


GODT
Global Observatory on Donation and Transplantation
WHO Collaborating Centre on Donation and Transplantation
GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD
ONT
HOME
ABOUT US
GLOBAL DATA
REFERENCE DOCUMENTS
LINKS
SEARCH
WHO-ONT
The global database on donation and transplantation represents the most comprehensive source to date of worldwide data concerning activities in organ donation and transplantation derived from official sources, as well as information on legal and organizational aspects.
The main direct collaboration between the World Health Organization (WHO) and the Spanish Transplant Organization, Organización Nacional de Trasplantes (ONT) has been focused on this collection of global data, which lead to the joint ONT-WHO Global Observatory on Donation and Transplantation.
READ MORE ...
173,727
ORGANS TRANSPLANTED ANNUALLY (2024)
2%
OF INCREASE OVER 2023
47,180
ACTUAL DECEASED ORGAN DONORS IN 2024
20
TRANSPLANTS/HOUR IN 2024

American Journal of Transplantation 2015; 15: 1141–1147
Wiley Periodicals Inc.

Minireview

Emerging Issues With Diagnosis and Management of Fungal Infections in Solid Organ Transplant Recipients

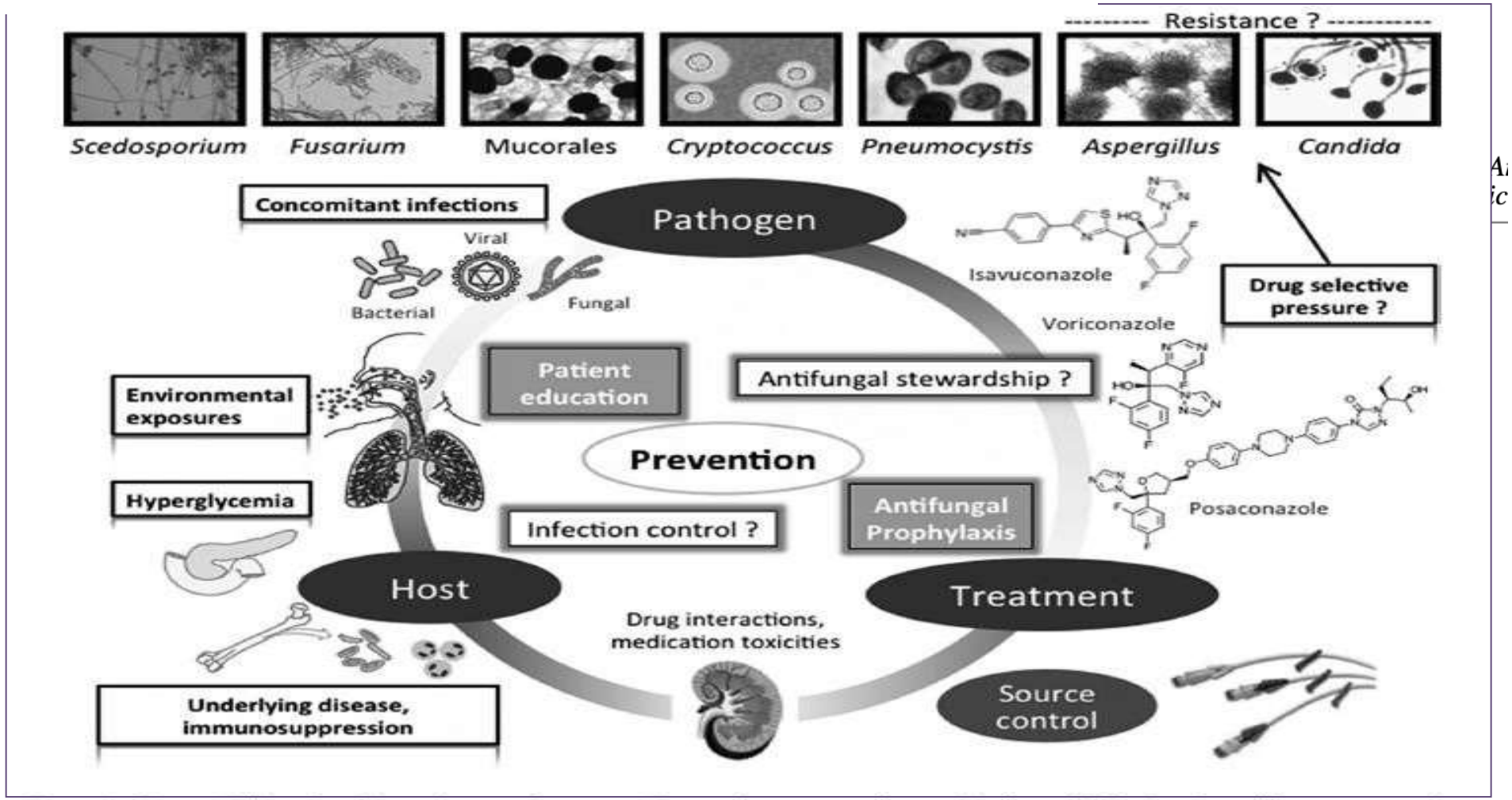


Figure 1: Factors influencing the pathogenesis, prevention, and treatment of emerging fungal infections in solid organ transplant recipients.

Invasive Fungal Infections among Organ Transplant Recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET)

Peter G. Pappas, Barbara D. Alexander, David R. Andes, Susan Hadley, Carol A. Kauffman, Alison Freifeld, Elias J. Anaissie, Lisa M. Brumble, Loreen Herwaldt, James Ito, Dimitrios P. Kontoyiannis, G. Marshall Lyon, Kieren A. Marr, Vicki A. Morrison, Benjamin J. Park, Thomas F. Patterson, Trish M. Perl, Robert A. Oster, Mindy G. Schuster, Randall Walker, Thomas J. Walsh, Kathleen A. Wannemuehler, and Tom M. Chiller[a]

- ABD'de 23 merkez, 15'i veri göndermiş
- 2001-2005 yılları, 16 808 SOT hastası
- 1063 hastada 1208 IFI
  - Candida %53, Aspergillus %19
  - 1 yıllık IA insidansı ≈ %0,6
- Bugünkü rehberlerin **epidemiyolojik omurgası**

Clinical Infectious Diseases 2010;50:1101–1111

Invasive Fungal Infections among Organ Transplant Recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET)

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Table 2. No. (%) of Invasive Fungal Infection (IFI) Cases in the Surveillance Cohort, by Transplant Type

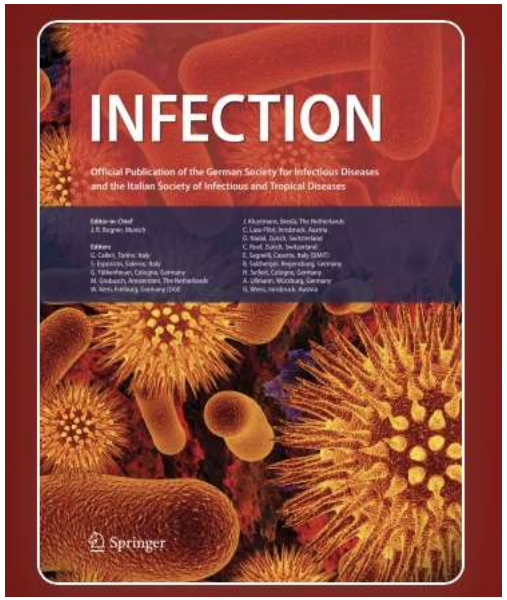
IFI type	Kidney (n = 332)	Liver (n = 378)	Pancreas (n = 128)	Lung (n = 248)	Heart (n = 99)	Small bowel (n = 22)
Candidiasis	164 (49)	255 (68)	97 (76)	56 (23)	48 (49)	19 (85)
Aspergillosis	47 (14)	42 (11)	6 (5)	109 (44)	23 (23)	0 (0)
Zygomycosis	8 (2)	9 (2)	0 (0)	8 (3)	3 (3)	0 (0)
Other mold	10 (3.0)	9 (2.4)	4 (3.1)	49 (19.8)	7 (7.1)	0 (0.0)
Unspecified mold	7 (2.1)	8 (2.1)	0 (0.0)	7 (2.8)	2 (2.0)	0 (0.0)
Cryptococcosis	49 (15)	24 (6)	6 (5)	6 (2)	10 (10)	1 (5)
Endemic mycoses	33 (10)	17 (5)	8 (6)	3 (1)	3 (3)	0 (0)
Pneumocystosis	5 (1)	0 (0)	1 (1)	4 (2)	3 (3)	0 (0)
Other yeast	6 (1.8)	9 (2.4)	5 (3.9)	0 (0.0)	0 (0.0)	1 (5)
Unspecified yeast	3 (0.9)	5 (1.3)	1 (0.8)	6 (2.4)	0 (0.0)	1 (5)

Infection (2025) 53:2411–2420
https://doi.org/10.1007/s15010-025-02575-z

RESEARCH

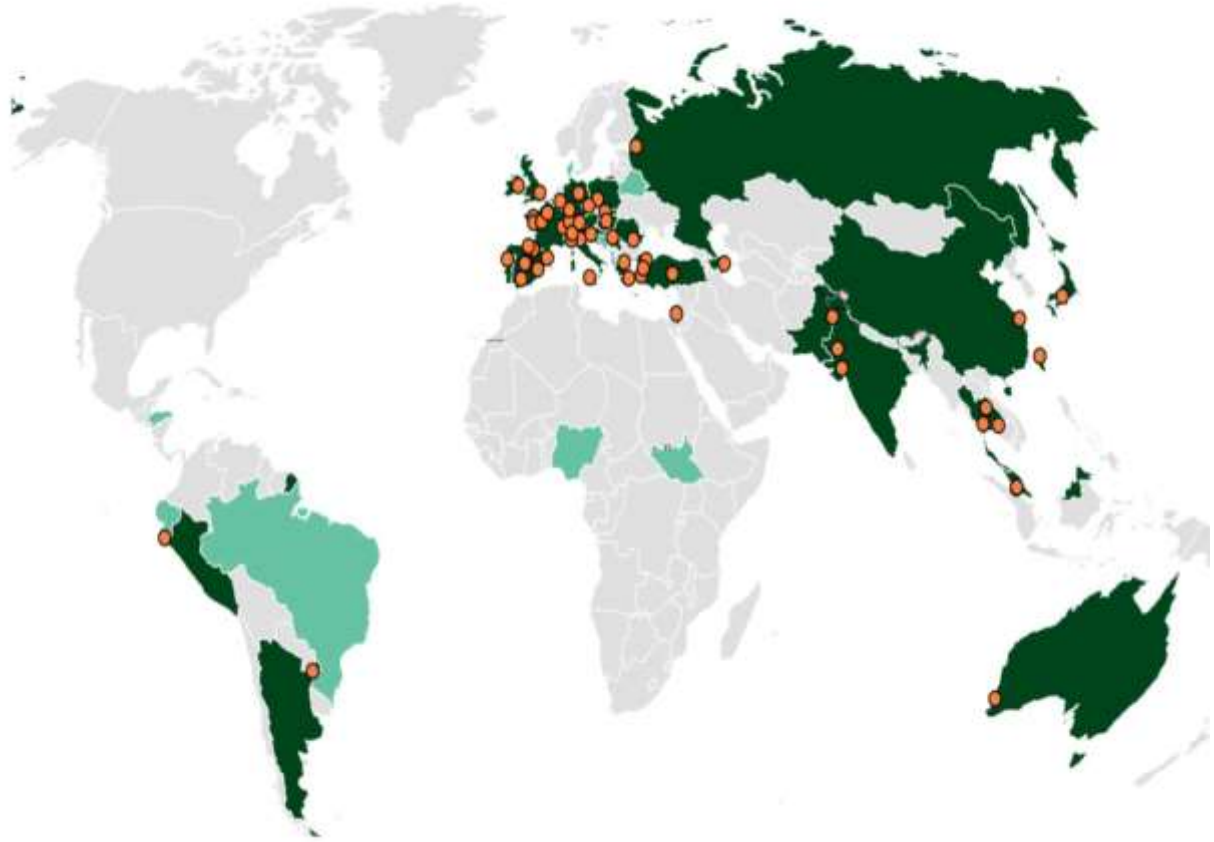
Current trends on antifungal prophylaxis in solid organ transplantation: a study from ESCMID-EFISG, ESCMID-ESGICH, SITA, and SEIMC-GESITRA-IC

Jon Salmanton-García[1,2,3,4,14] · Alessandro Giacinta[5,6] · Maddalena Giannella[7,8] · Antonio Vena[9,10] · Patricia Muñoz[5,11,12,13] · Oliver A. Cornely[1,2,3,4,14] · Maricela Valerio[5,11,12,13]



- **Çevrimiçi anket (Mayıs 2023–Mayıs 2024)**
- 64 **tersiyer bakım kurumu** (32 ülke; çoğunluk Avrupa) katıldı
- Toplanan veriler:
  - Transplant hacmi (organ türü)
  - İFİ insidansı ve etken patojenler
  - Antifungal profilaksi stratejileri *başlama kriterleri, tercih edilen ajanlar ve süre* bilgilerini içeriyordu

Current trends on antifungal prophylaxis in solid organ transplantation: a study from…



- Universal profilaksi yaygın
- Hedefe yönelik / risk temelli

Uygulamalar rehberlerden çok lokal epidemiyoloji ve merkez deneyimiyle şekillenmektedir…

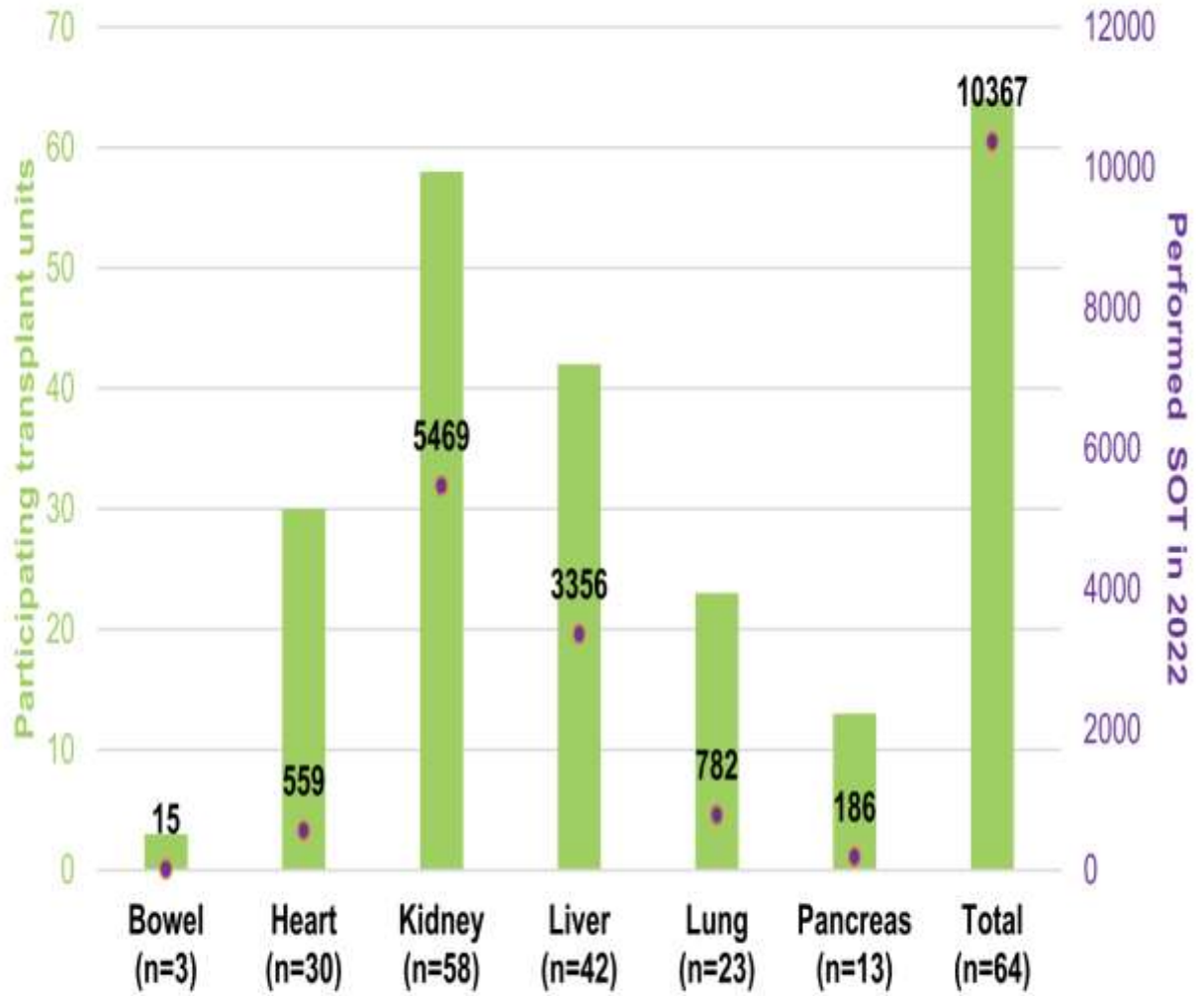


Fig. 2 Participating institutions by organ and the number of transplantations performed for each organ in 2022

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Patricia Muñoz[5,11,12,13] · Oliver A. Cornely[1,2,3,4,14] · Maricela Valerio[5,11,12,13]

Total: 10.362 nakil
Böbrek: 5469
Karaciğer: 3356

Infection (2025) 53:2411–2420
https://doi.org/10.1007/s15010-025-02575-z

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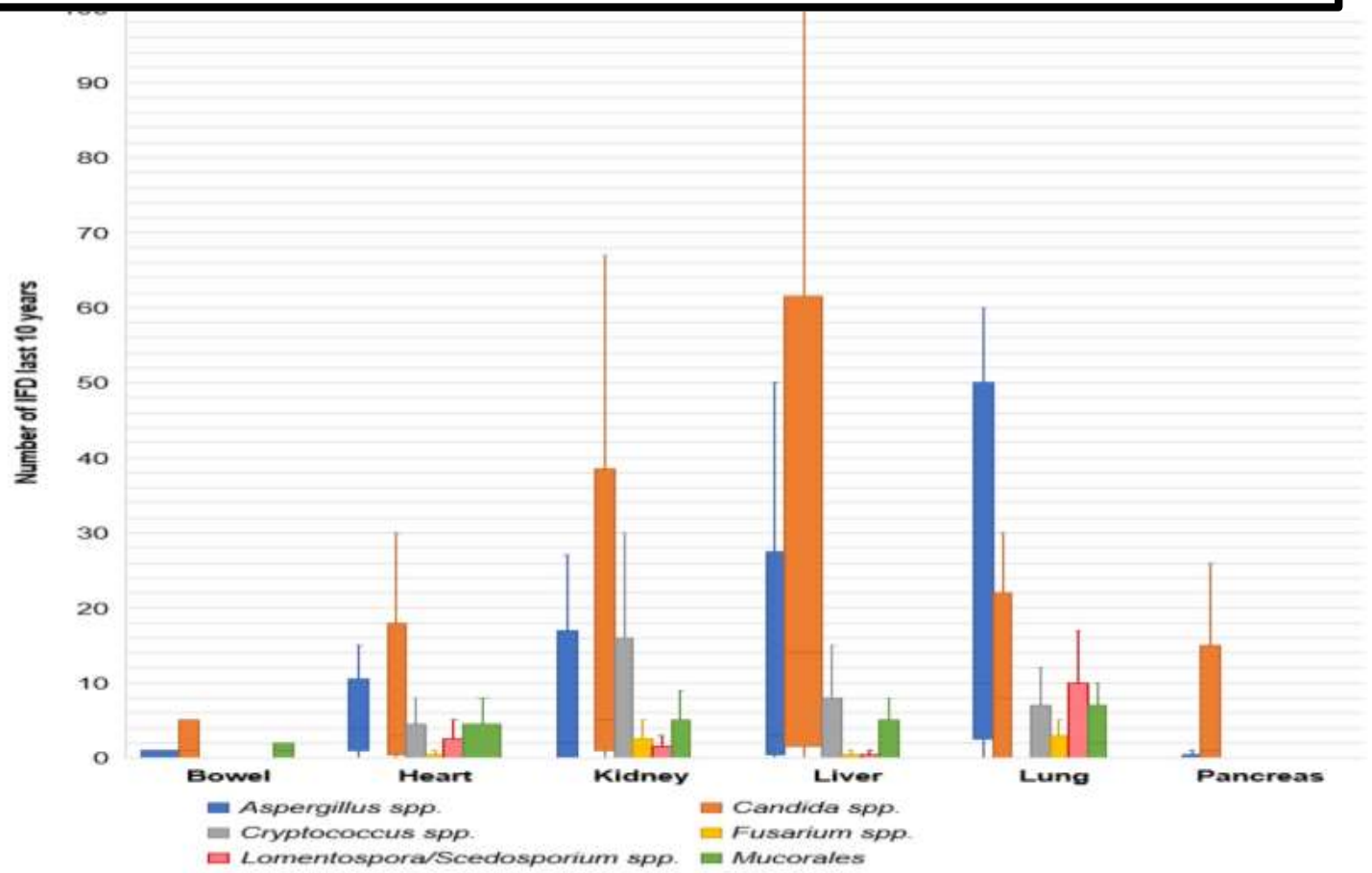

- **Karaciğer:** *Candida spp.*
- **Akciğer:** *Aspergillus spp.*
- **Kalp:** *Candida spp*, *Aspergillus spp*
- **Böbrek:** *Candida* (daha nadir)
- **Pankreas:** *Candida spp.*

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Nakil Türü	Profilaksi Yaklaşımı	Sıklıkla Kullanılan Tetikleyiciler	Tercih Edilen Ajanlar
Akciğer	Çoğunlukla **universal profilaksi**	Erken post-transplant dönem	Liposomal AmB, azoller
Karaciğer	**Hedefe yönelik profilaksi**	Reoperasyon, *Candida* kolonizasyonu	Flukonazol, L-AmB
Kalp	**Risk temelli / hedefe yönelik**	Yoğun bakım, yeniden girişim	Flukonazol
İnce barsak	Sıklıkla profilaksi uygulanır	Mukozal hasar, kolonizasyon	Flukonazol, L-AmB
Böbrek	Nadiren / seçilmiş olgularda	Ciddi komplikasyonlar	Standart yaklaşım yok

Salmanton-García ve ark., *Infection*, 2025

Antifungal profilaksi uygulamaları, en homojen şekilde akciğer naklinde, en heterojen şekilde ise böbrek naklinde görülmektedir..

Ana Bulgular ve Klinik Çıkarımlar

  - **Solid organ naklinde universal antifungal profilaksi standart değildir**
  - **Organ-spesifik ve risk-temelli yaklaşımlar** ön plandadır
- En sık tercih edilen antifungal ajanlar:
  - **Liposomal amfoterisin B**
  - **Flukonazol**
- Merkezler arası uygulama farklılıklarının temel nedenleri:
  - Güçlü kanıt eksikliği
  - Değişen fungal epidemiyoloji
  - Tanı yöntemlerindeki gelişmeler
  - Yeni antifungal ajanların kullanıma girmesi
- **Standart, kanıta dayalı ve uyumlaştırılmış rehberlere**

Risk faktörleri: kimler "yüksek risk"?

Genel (tüm SOT)

- Rejeksiyon atakları, yüksek doz steroid, ATG
- CMV hastalığı/reaktivasyonu
- Uzamış ICU, ventilasyon, geniş spektrum AB, TPN
- Santral kateter, HD, reoperasyon
- Nötropeni/lenfopeni,

Organ-spesifik ipuçları

- Akciğer: Aspergillus kolonizasyonu, bronş anastomoz iskemisi/nekrozu
- Karaciğer: biliyer kaçak/komplikasyon, reoperasyon, renal yetmezlik
- Pankreas/barsak: anastomoz sorunları,

Profilaksi stratejileri

Profilaksi stratejileri

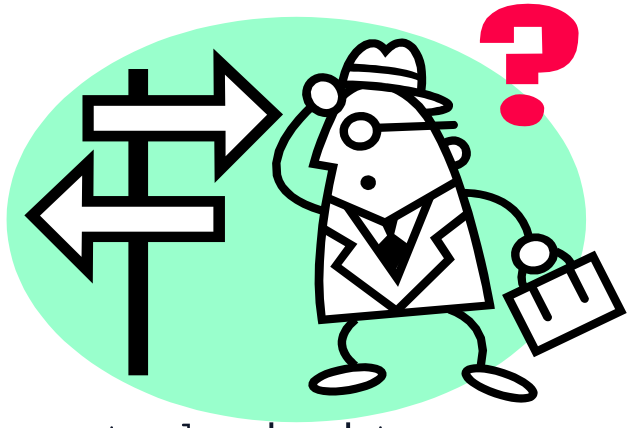
Universal profilaksi: Belirli nakil tipinde tüm alıcılara (örn. akciğer naklinde anti-küf)

Hedefe yönelik (targeted) profilaksi: Sadece yüksek riskli alt gruba (karaciğerde seçilmiş hastada Candida riski)

Pre-emptive: seri tarama (kültür/antijen/BT/BAL) + erken tedavi

Profilaksi Stratejileri

- Seçimi belirleyen 4 ana eksen:
  - Hasta riski + organ tipi
  - Merkez epidemiyolojisi/direnç
  - İlaç-ilaç etkileşimleri (CNI/mTOR) ve toksisite
  - Uygulanabilirlik (TDM, inhaler uygulama, takip)

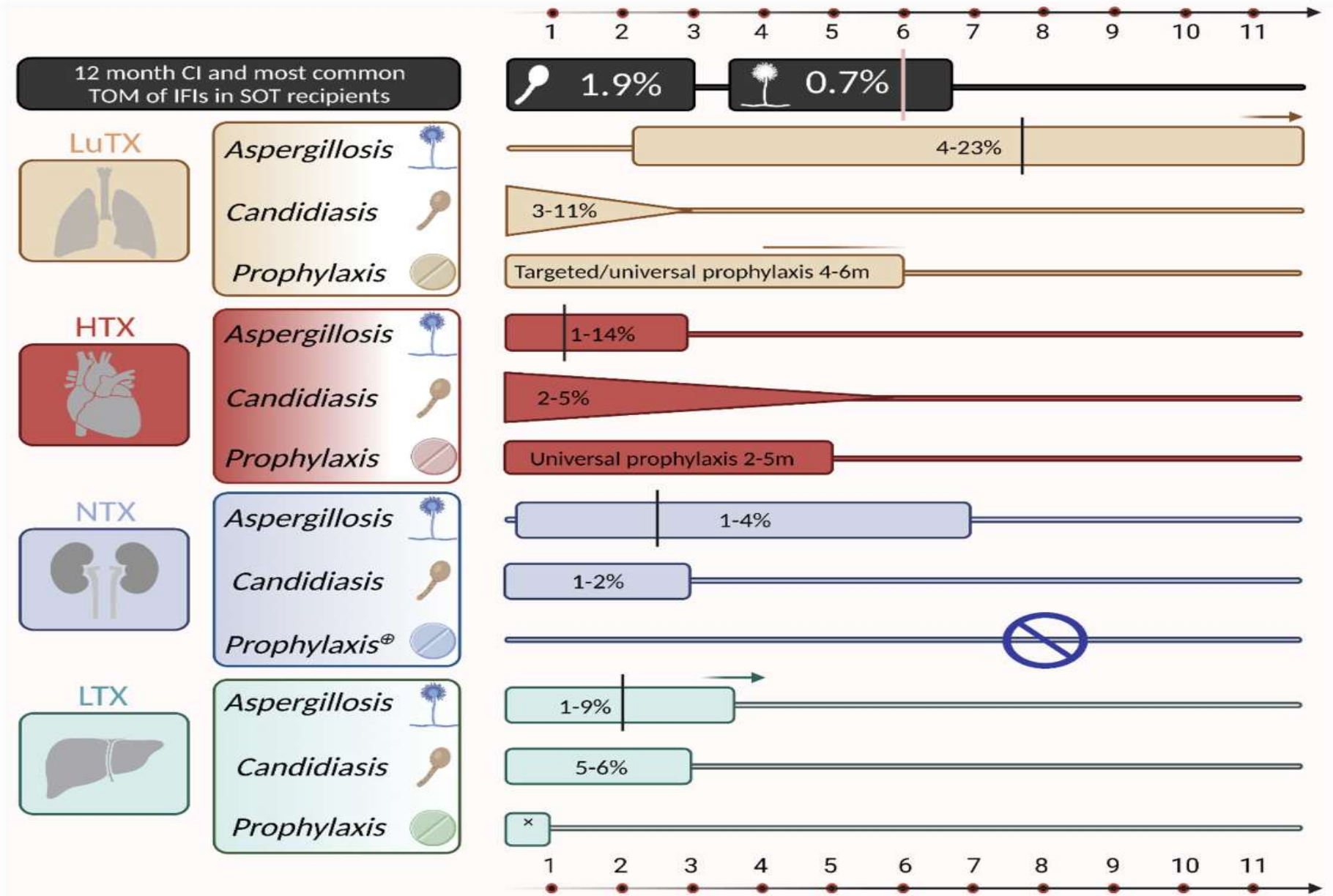


Organ bazlı profilaksi: pratik cerceve

Proportions of fungal pathogens causing invasive fungal infection in solid organ transplant recipients categorized by transplantation

	Candida spp.	*Aspergillus* spp.	*Cryptococcus* spp.	Pneumocystis	Other
SOT-recipients overall[7-10]	39%-59%	19%-34%	1%-8%	7%-11%	9%-15%
Kidney[7,8,10,63,64]	24%-61%	12%-36%	3%-19%	0%-16%	4%-31%
Liver[7,8,10,65,66]	20%-80%	6%-67%	0%-7%	0%-3%	0%-15%
Lung[7,8,10,67,68]	23%-62%	27%-67%	0%-2%	0%-2%	12%-29%
Heart[7,8,10,11,69]	27%-65%	22%-50%	0%-10%	0%-5%	8%-30%
Pancreas; pancreas–kidney[7,8,10,70]	67%-81%	0%-11%	0%-33%	0%-9%	0%-12%
Small bowel[8]	85%	0%	5%	0%	10%

Kriegl L,et al. Transpl Infect Dis. 2022;24:e13855



Kriegl L,et al. Transpl Infect Dis. 2022;24:e13855

KANDİDA ENFEKSİYONLARI

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

ESCMID PUBLICATIONS 10.1111/1469-0691.12038

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: diagnostic procedures

REVIEW 10.1111/1469-0691.12660

Invasive fungal infections in solid organ transplant recipients

J. Gavaldà[1], Y. Meije[1], J. Fortún[2], E. Roilides[3], F. Saliba[4], O. Lortholary[5], P. Muñoz[6,7,8,9], P. Grossi[10], M. Cuenca-Estrella[11] on behalf of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH)

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION WILEY

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Candida infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

of Practice

Review > Lancet Infect Dis. 2025 May;25(5):e280-e293.

doi: 10.1016/S1473-3099(24)00749-7. Epub 2025 Feb 13.

Global guideline for the diagnosis and management of candidiasis: an initiative of the ECMM in cooperation with ISHAM and ASM

American Journal of Transplantation 25 (2025) 2634–2645

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Original Article

Invasive *Candida* infections in solid organ transplant recipients between 2008 and 2020

- Retrospektif, çok merkezli kohort çalışması, Swiss Transplant Cohort Study bünyesinde yer almakta olup, **2008–2020 yılları arasında** SOTr'de invaziv kandidiyazisin epidemiyolojisini ve klinik sonuçlarını incelemektedir

- Toplam **4755 hasta** arasında **205 hastada (%4,3)** toplam **262 invaziv kandidiyazis atağı** saptanmıştır
- İnvaziv kandidiyazisin **bir yıllık kümülatif insidansı %2,8** (%95 güven aralığı [GA], 2,4–3,3) olup, çalışma süresi boyunca **anlamlı şekilde azalma göstermiştir** (*P* = 0,046)

- Enfeksiyonların büyük bölümü **nakilden sonraki ilk yıl içinde** ortaya çıkmıştır (**%65,3; 171/262**)

American Journal of Transplantation 25 (2025) 2634–2645

Contents lists available at ScienceDirect

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journal homepage: www.amjtransplant.org

Original Article

Invasive *Candida* infections in solid organ transplant recipients between 2008 and 2020

- **Kandidemi,** intraabdominal enfeksiyonlara ve diğer enfeksiyon odaklarına kıyasla **daha nadir** görülmüştür

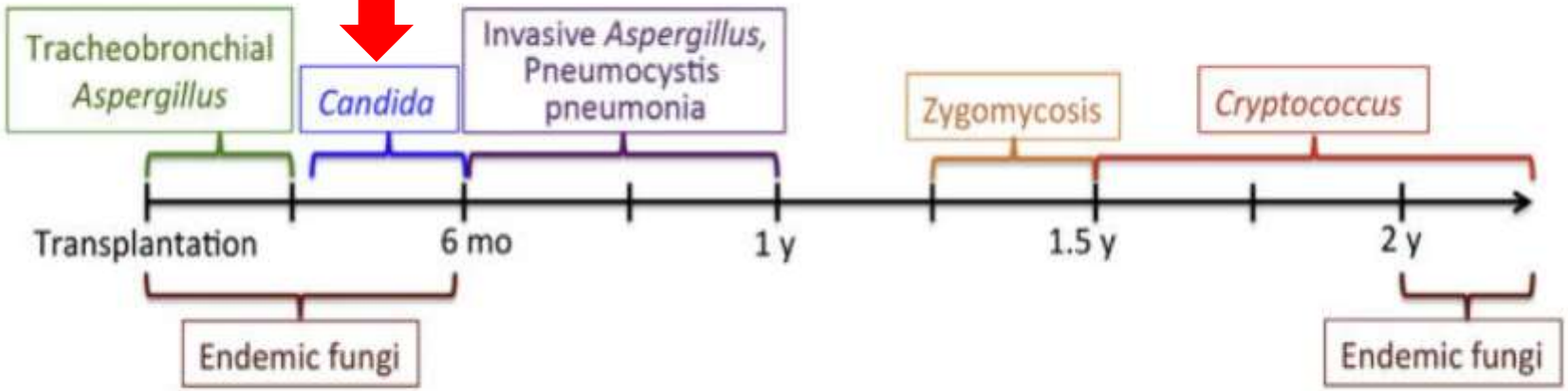
- En sık izole edilen etken **Candida albicans** olup (**%69,6; 181/262**), bunu **Candida glabrata** izlemiştir (**%27,4; 32/117**)

- **Tüm nedenlere bağlı 12 haftalık mortalite %23,5** olarak saptanmış; bu oran **karaciğer (%34,5)** ve **kalp (%30)** nakli alıcılarında en yüksek düzeydedir.

- **Kandidemi, %51,1'lik 12 haftalık mortalite oranı** ile ilişkili bulunmuş ve özellikle **nakilden sonraki ilk 3 ay içinde gelişti̇ğinde, 1 yıllık post-transplant mortaliteyi anlamlı derecede artırmıştır**

Epidemiology of invasive fungal infection in solid organ transplant recipients

Organ Transplanted	IFIs in Order of Decreasing Frequency
Kidney	*Candida* > *Crypto* > *Aspergillus* > Endemic mycoses > Molds > PJP
Liver	*Candida* > *Aspergillus* > *Crypto* > Endemic mycoses > Molds > PJP
Pancreas	*Candida* > Endemic mycoses > *Aspergillus* ≈ *Crypto* > Molds > PJP
Lung	*Aspergillus* > *Candida* > Molds > *Crypto* > PJP > Endemic mycoses
Heart	*Candida* > *Aspergillus* > Molds > *Crypto* > Endemic mycoses > PJP
Small bowel	*Candida* > *Crypto* > *Aspergillus* > Endemic mycoses > Molds > PJP



Anesi JA. Infect Dis Clin North Am . 2016 30(1): 277-296

REVIEW 10.1111/1469-0691.12660

Invasive fungal infections in solid organ transplant recipients

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Risk factors for invasive candidiasis

Transplant type	Target population
Liver	**High-risk liver transplant recipients:** **Major:** MELD score >30 Re-transplantation, fulminant hepatic failure, Renal failure requiring replacement therapy, **Minor:** MELD score 20–30, split, living-donor >40 transfusion blood products, choledochojejunostomy (Roux-en-Y) Renal failure not requiring replacement therapy (CrCl <50 mL/min) Early re-intervention, multifocal colonization/infection by *Candida* spp.
Pancreas	Post-perfusion pancreatitis, acute rejection and poor initial allograft function Vascular thrombosis, enteric drainage, anastomotic problems, haemodialysis Laparotomy after transplantation
Intestinal	Acute rejection and poor initial allograft function, haemodialysis, laparotomy after transplantation, anastomotic problems, over-immunosuppression
Heart	Acute rejection, haemodialysis, re-exploration after transplantation

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Candida infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Saima Aslam[1] | Coleman Rotstein[2] | on behalf of the AST Infectious Disease Community of Practice

Infection—invasive candidiasis	Therapy		Comments
	Initial	Alternative	
Candidemia and invasive candidiasis	Echinocandin (Caspofungin 70 mg loading dose then 50 mg IV daily; Micafungin 100 mg IV daily; or Anidulafungin 200 mg loading dose then 100 mg IV daily)	Fluconazole 12 mg/kg loading dose and then 6 mg/kg IV/PO daily if clinically stable and unlikely to have fluconazole resistance	For candidemia duration of therapy is 14 d after negative blood cultures For invasive candidiasis duration of therapy may be for at least 2 wk and potentially longer until resolution of signs and symptoms Transition of echinocandin to oral fluconazole (after 5-7 d) if stable, clearance of blood stream and fluconazole susceptible

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Saima Aslam[1] | Coleman Rotstein[2] | on behalf of the AST Infectious Disease Community of Practice

Oropharyngeal mild moderate	Clotrimazole troche 10 mg X5/d Fluconazole 400 mg X1 d then 200 mg daily po	Nystatin 500,000 units qid Itraconazole solution 200 mg daily po or posaconazole suspension 400 mg BID po X3 d then 400 mg daily	Duration of therapy 14 d Duration up to 28 d
Esophageal	Fluconazole 200-400 mg po or IV daily Fluconazole refractory—Itraconazole solution 200 mg daily po or voriconazole 3 mg/kg q12h po or IV daily	Echinocandin (Caspofungin 70 mg loading dose the 50 mg IV daily; Micafungin 150 mg IV daily; or Anidulafungin 200 mg IV daily)	Duration of therapy 14-21 d

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Endovascular infection	L-AmB 3-5 mg/kg IV daily	High dose echinocandin (Caspofungin 150 mg, micafungin 150 mg or anidulafungin 200 mg IV daily)	Prolonged duration (for 6 wk after valve replacement) or chronic suppressive therapy
Implantable cardiac device infection	L-AmB 3-5 mg/kg IV daily	High dose echinocandin (Caspofungin 150 mg, micafungin 150 mg or anidulafungin 200 mg IV daily)	For 4 wk after device removal and if not removed chronic suppressive therapy Can de-escalate therapy to fluconazole if strain susceptible

Clinical TRANSPLANTATION
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Saima Aslam[1] | Coleman Rotstein[2] | on behalf of the AST Infectious Disease Community of Practice

Urinary tract infection	Fluconazole susceptible—fluconazole 200 mg po daily	AmB 0.3-0.6 mg/kg IV per d	Duration of therapy 14 d for symptomatic infection Therapy duration for AmB 1-7 d For asymptomatic candiduria at time of stent removal up to 7 d

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Candida infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Saima Aslam[1] | Coleman Rotstein[2] | on behalf of the AST Infectious Disease Community of Practice

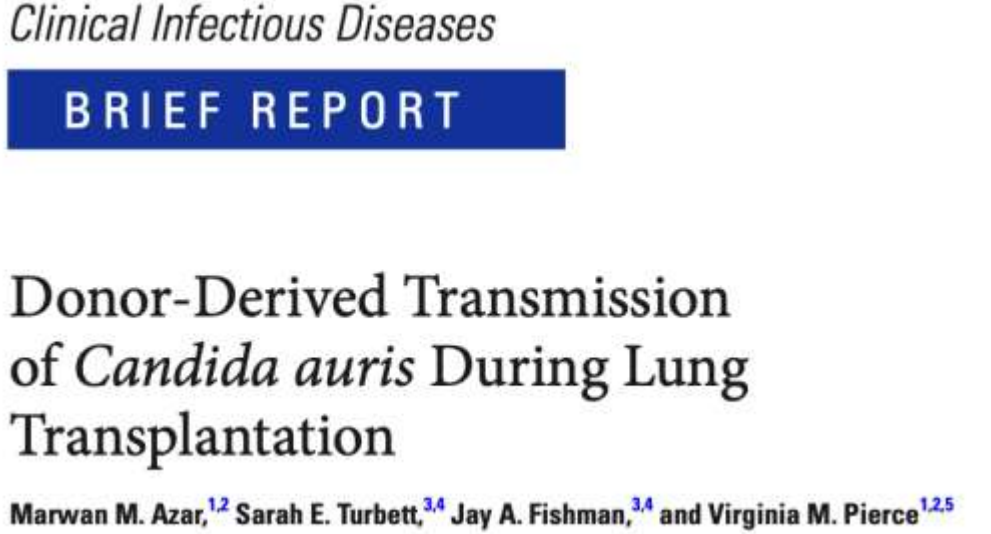
Empiric therapy for suspected IC in the ICU (presence of persistent fever, *Candida* colonization and other risk factors for IC)	Echinocandin (Caspofungin 70 mg loading dose the 50 mg IV daily; micafungin 100 mg IV daily; or anidulafungin 200 mg loading dose then 100 mg IV daily) if hemodynamically unstable	Fluconazole 12 mg/kg loading dose IV then 6 mg/kg daily if not colonized with fluconazole-resistant strain and hemodynamically stable	Duration of therapy for up to 2 wk

	Liver transplant[a]	Lung transplant	Heart transplant
Inhaled Ampb	-	2C	-
Lip AmpB	2B	-	-
Posaconazole/Isavuconazole	-	2C	-
Voriconazole	2C[b]/1A[c]	1C	1C
Fluconazole	1B	-	-
Itraconazole	-	1C	1C
Echinocandine	2C[b]/1A[c]	-	1C

> Transpl Infect Dis. 2022 Oct;24(5):e13919. doi: 10.1111/tid.13919.

Challenges and opportunities in stewardship among solid organ transplant recipients with Candida auris bloodstream infections

Christine A Vu [1], Adriana Jimenez [2 3], Shweta Anjan [4 5], Lilian M Abbo [2 4 5]



Clinical Infectious Diseases

BRIEF REPORT

Donor-Derived Transmission of *Candida auris* During Lung Transplantation

Marwan M. Azar,[1,2] Sarah E. Turbett,[3,4] Jay A. Fishman,[3,4] and Virginia M. Pierce[1,2,5]

The Journal of Infectious Diseases

PERSPECTIVE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

The *Candida auris* Alert: Facts and Perspectives

Frederic Lamoth[1,2] and Dimitrios P. Kontoyiannis[3]

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- ***C. auris*** çok kolay çevresel persiste olabilir ve **nosokomial yayılım** yapabilir; bu nedenle **enfeksiyon kontrol** çok önemlidir
- Başlangıçta **ekinokandinler (micafungin/anidulafungin/kaspofungin)** önerilir
- Direnç gelişimi veya tedavi başarısızlığında **liposomal amfoterisin B** düşünülebilir
- Kombinasyon tedavisi için kanıt

Kandidemi / invaziv kandidiyazis

- Başlangıç (özellikle kritik hasta/azol maruziyeti): ekinokandin temelli yaklaşım sıklıkla tercih edilir
- Klinik stabilit… flukonazol/azol…
- Kaynak kontroli… sorunları) mort…
- Tedavi süresi: …üzelme esas; metastatik odak varsa uzatılır
- SOT özelinde: organ komplikasyonları ve immünsüpresyon düzeyi tedaviyi belirler

Kandidemi yönetimi; erken ekinokandin tedavisi+ agresif kaynak kontrolü + dikkatli step-down stratejisi üzerine kuruludur…

İNVAZİV ASPERGİLLOZİS (İA)

SPECIAL ISSUE: TRANSPLANT INFECTIOUS DISEASES

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Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Neofytos et al. BMC Infectious Diseases (2021) 21:296
https://doi.org/10.1186/s12879-021-05958-3

BMC Infectious Diseases

GUIDELINES Open Access

Invasive aspergillosis in solid organ transplant patients: diagnosis, prophylaxis, treatment, and assessment of response

Dionysios Neofytos[1*], Carolina Garcia-Vidal[2], Frédéric Lamoth[3,4], Christoph Lichtenstern[5], Alessandro Perrella[6,7] and Jörg Janne Vehreschild[8,9,10]

Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

REVIEW 10.1111/1469-0691.12660

Invasive fungal infections in solid organ transplant recipients

J. Gavaldà[1], Y. Meije[1], J. Fortún[2], E. Roilides[3], F. Saliba[4], O. Lortholary[5], P. Muñoz[6,7,8,9], P. Grossi[10], M. Cuenca-Estrella[11] on behalf of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH)

İnvaziv Aspergillozis

- IA nadir ama mortalitesi yüksek
- Graft ve hasta sağkalımına ciddi etkisi
- Ortak riskler
- Organ-spesifik farklılıklar
- Nötropenik hastaya göre düşük tanısal performans
- Yüksek kl

SOT alıcılarında invaziv aspergillozis, nakle özgü tanısal ve terapötik stratejiler gerektiren, kendine özgü bir klinik sendromu temsil eder

Neofytos et al. BMC Infectious Diseases (2021) 21:296
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Population	Incidence (%)	Overall mortality (%)
Heart	3.5–26.7	36–66.7
Kidney	1.2–4	4–25
Liver	1–4.7	83–88
Lung	8.3–23.3	4.2

	Risk factors
Heart	Reoperation; CMV infection; post-transplantation hemodialysis; presence of another patient with IA in the transplant program 2 months before or after the procedure; rejection, admission to the ICU, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO)
Kidney	Bloodstream infections; pre-transplant chronic pulmonary obstructive disease; impaired graft function; long-term dialysis prior to transplantation; serious post-transplant infections
Liver	MELD score, choledochojejunostomy; anastomosis; bacterial infections in the first month and absence of antifungal prophylaxis; cytomegalovirus (CMV) reactivation; renal failure; hemodialysis; re-transplantation or transplantation for fulminant hepatic failure; reoperation
Lung	Single lung transplantation; pre- and post-transplant colonization with *Aspergillus* spp., early airway ischemia, CMV infection, rejection

Antifungal Profilaksi: Genel Yaklaşım (SOT)

- **SOT alıcılarında rutin primer antifungal profilaksi** genel olarak **önerilmemektedir**

- Antifungal profilaksi stratejileri, **transplant merkezleri arasında belirgin farklılıklar** göstermektedir.

Peghin M, et al. Transpl Int. 2016;29(1):51-62

Perrella A, et al. Infect Dis. 2016;48(2):161-6

Perrella A, et al. Transplant Proc. 2012;44(7):1977-81

SOT'ta Neden Universal Profilaksi Yok?

- **Kanıtlar ve sınırlılıklar**
  - SOT popülasyonunda:
  - İnvaziv aspergillozis (IA) ve diğer invaziv küf enfeksiyonlarının **insidansı düşüktür**
  - Enfeksiyonların **nakil sonrası ortaya çıkış zamanı değişkendir**
  - Profilaksinin invaziv küf enfeksiyonlarını önlemedeki etkinliğini gösteren **güçlü kanıtlar sınırlıdır**
- Bu nedenlerle, **çoğu merkezde universal antifungal profilaksi uygulanmamaktadır**
- Karaciğer nakli alıcılarında, IA için önceden tanımlanmış risk faktörlerine dayalı antifungal profilaksiyi değerlendiren **prospektif randomize bir çalışma,**
  - **IA insidansının düşük olması nedeniyle** anlamlı klinik fayda gösterememiştir.

Peghin M, et al. Transpl Int. 2016;29(1):51-62

Perrella A, et al. Infect Dis. 2016;48(2):161-6

Perrella A, et al. Transplant Proc. 2012;44(7):1977-81

Winston DJ, et al. Am J Transplant. 2014;14(12):2758-64

Organ-Spesifik Profilaksi Yaklaşımları

Güncel klinik uygulamalar:

- **Aerosolize amfoterisin B lipid kompleks:**
  - Cerrahi sonrası **ilk 18 güne kadar** kullanıldığında
  - Küf enfeksiyonlarına karşı **yararlı bulunmuştur**
- **Pre-emptive antifungal tedavi:**
  - Güncel olarak **sadece akciğer nakli alıcılarında** önerilmektedir
- **Hedefe yönelik (targeted) profilaksi:**
  - **Karaciğer ve kalp nakli alıcılarında** tercih edilen yaklaşımdır
- Mevcut kanıtların büyük bölümü:
  - **Retrospektif kohort** ve
  - **Olgu-kontrol çalışmalarına** dayanmaktadır

Husain S, et al. Clin Transpl. 2019;33(9):e13544

Peghin M, et al. Transpl Int. 2016;29(1):51-62

Perrella A, et al. Infect Dis. 2016;48(2):161-6

Perrella A, et al. Transplant Proc. 2012;44(7):1977-81

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Primary therapy

Voriconazole	6 mg/kg IV/PO[a] every 12 h for 1 d, followed by 4 mg/kg IV/PO every 12 h	Target trough level for treatment is >1 mg/L.[179,180,184] A level of 1-5.5 mg/L is considered adequate for most patients. A higher target (eg, 2-6 mg/L) should be used if there is disease with a poor prognosis (eg, CNS infection, bulky disease, multifocal infection); infections with pathogen with elevated MICs (eg, an MIC of 2 mg/L)[128]	Due to accumulation of the IV vehicle (cyclodextrin), the manufacturer recommends the use of oral voriconazole in patients with CrCl <50 mL/min. In clinical practice, however, IV voriconazole has been safely administered to patients with different degrees of renal failure[209,210]
		Once steady-state levels have been reached, repeat sampling is warranted every 3-5 d[184] in unstable patients and when there is uncertainty about voriconazole concentrations	Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended
		Measurement of serum trough concentration within 5-7 d	Non-linear (ie, highly variable) pharmacokinetics

- Vorikonazol TDM
- Sirolimus, tacrolimus, siklosporin TDM
- KCFT takibi
- EKG

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Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Alternative therapies			
Isavuconazole	372 mg (isavuconazole 200 mg) IV/PO[a] every 8 h for 6 doses, followed by 372 mg (isavuconazole 200 mg) IV/PO once daily	Trough level in the range of 2-3 mg/L (mean concentration range from phase II/III clinical studies) after day 5 suggests adequate drug exposure[128] No apparent relationship between exposure and efficacy to support routine TDM for isavuconazole[183] Has 130-h half-life—long clearance after discontinuation	Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended Dose adjustment is not required in renal impairment Linear pharmacokinetics with low interpatient variability[136]
Liposomal amphotericin B (AmBisome®)	3-5 mg/kg/d IV	There is currently insufficient evidence to support the routine use of TDM	Monitoring of electrolytes, and renal and hepatic function is recommended Higher dosages are not more effective Better tolerated than Abelcet®
Amphotericin B Lipid Complex (Abelcet®)	5 mg/kg/d IV	There is currently insufficient evidence to support the routine use of TDM	Monitoring of electrolytes, and renal and hepatic function is recommended Higher dosages are not more effective

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Anidulafungin	200 mg IV on day 1 and 100 mg IV daily thereafter	There is currently insufficient evidence to support the routine use of TDM	It has been evaluated only as salvage therapy. Its role as single-agent therapy is controversial It does not require dosage adjustments in patients with renal or hepatic dysfunction
Caspofungin	70 mg IV on day 1 and 50 mg IV/d thereafter		It has been evaluated only as salvage therapy. Its role as single-agent therapy is controversial. Monitoring of hepatic function is recommended Dose adjustment is not required in renal impairment Drug interactions are less clinically important
Micafungin	100-150 mg IV daily	There is currently insufficient evidence to support the routine use of TDM	Monitoring of hepatic function is recommended Non-FDA-approved use (for treatment of IA) Dose adjustment is not required in renal impairment Drug interactions are less clinically important

- Tek ajan kullanımı ??
- Salvage terapi

İnvaziv Pulmoner Aspergiloz: Kurtarma Tedavisi

- Amfoterisin-B lipid kompleks, 5 mg/kg/gün IV
- Kaspofungin 70 mg/gün ilk doz, sonra 50 mg/gün IV
- Mikafungin 100-150 mg/gün IV
- Posakonazol
  - Oral süspansiyon: 3x200mg
  - Tablet ilk gün: 2x300mg, sonra 300 mg/gün
  - IV: ilk gün 2x300 mg/gün, sonra 1x300mg/gün
- Itrakonazol süspansiyon 2x200mg

IDSA, Practice Guidelines for the Diagnosis and Management of Aspergillosis,CID 2016:63

İnvaziv Pulmoner Aspergilloz: Kurtarma Tedavisi

- İdeal kombinasyon?
- İdeal antifungal dozu?
- İlaç etkileşimleri ?
- Tedavinin maliyet-etkinliği?

IDSA, Practice Guidelines for the Diagnosis and Management of Aspergillosis,CID 2016:63

İnvaziv Pulmoner Aspergilloz:Kombinasyon Tedavisi

- Rutin önerilmez
- Amaç aditif ve sinerjik etki
- Olası yararlar
  - İlaç direncinin azaltılması
  - Tedavi süresinin kısaltılması
  - Toksisiteyi azaltmak amacıyla dozun düşürebilmesi

IDSA, Practice Guidelines for the Diagnosis and Management of Aspergillosis,CID 2016:63

İnvaziv Pulmoner Aspergilloz

- Tedavi süresi: En az 12 hafta
- Değerlendirme
  - İmmünsüpresyonun seviye ve süresi
  - Tutulum alanı
  - Tedaviye yanıt

Güçlü öneri, düşük kaliteli kanıt

IDSA, Practice Guidelines for the Diagnosis and Management of Aspergillosis,CID 2016:63

Akciğer Nakli Hastalarında Trakeobronşiyal Aspergilloz

- Saprofitik olanlar dahil tedavi edilmeli (tıkayıcı bronşiyal aspergilloz, endobronşiyal aspergilloz, mukoid impaksiyon)
- Tedavi: inhaler AmB önerilir
  - Anastomotik endobronşiyal iskemi
  - İskemi reperfüzyon hasarı
- Tedavi süresi en az üç ay ya da iyileşene kadar

Güçlü öneri, orta kaliteli kanıt

İnvaziv aspergillozis (IA)

- SOT'ta en sık invaziv küf; akciğer nakli alıcılarında
- İlk seçenek yaklaşımı: vorikonazol; klinik bağlama göre alternatif azoller veya liposomal amfoterisin B
- Başarı için "paket": erken tanı + uygun antifungal + TDM + etkileşim yönetimi + odak kontrolü
- Kombinasyon tedavisi: seçilmiş ağır

Mukormikoz (Mucorales)

- Yüksek mortalite; tanı gecikmeye eğilimli → hızlı ilerler
- Acil görüntüleme + doku tanısı+ agresif cerrahi debridman + etkin antifungal tedavi
- Predispozan faktörlerin düzeltilmesi: immünsüpresyon optimizasyonu, hiperglisemi/asidoz vb.
- İlk seçenek: yüksek doz liposomal amfoterisin B; uygun olguda posakonazol/isavukonazol ardışık/alternatif olabilir

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Emerging fungal infections in solid organ transplant recipients: Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

Fungal pathogen (references)	Initial therapy	Alternative therapy
Mucormycetes	Surgical excision/debridement is recommended for all infections outside of lungs Induction therapy: • LF-AmB is the treatment of choice (Strong, Moderate) • Combination of an echinocandin + LF-AmB may be considered based on animal studies and retrospective reports [129,130] (Weak, Very Low) • AmB deoxycholate was historically the drug of choice but is associated with substantial nephrotoxicity and generally avoided in the current era [80,132,133] (Strong, Moderate) Maintenance therapy: • Posaconazole or isavuconazonium[a] sulfate (Weak, Moderate)	Induction therapy: • Posaconazole or isavuconazonium sulfate[a] for patients intolerant to or failing LF-AmB [86,134,135] (Weak, moderate) • Combination of posaconazole + LF-AmB may be considered in refractory infections, but data are conflicting (Weak, Very Low) Maintenance therapy: • LF-AmB in patients who are clinically unstable or unable to tolerate oral intake
Fusarium [137]	Surgical excision or debridement is recommended whenever feasible • Voriconazole (Weak, Low)	• Combination therapy (LF-AmB + voriconazole[b]) may be considered pending final identification and susceptibility data. Goal is to provide coverage for organisms resistant to one or the other of these agents. (Weak, Low) • Posaconazole (Weak, Low) • *Fusarium solani* and *Fusarium verticilloides* may be resistant to voriconazole and require LF-AmB (Weak, Low)
Scedosporium	Surgical excision or debridement is recommended whenever feasible • Voriconazole[b] [88,89] (Weak, Low)	• Combination of an echinocandin and voriconazole may be considered (Weak, Very Low)

Kriptokokkoz

- SOT alıcılarında kriptokokkoz genellikle **nakilden ≥6 ay sonra** ortaya çıkar
- Etkenlerin büyük çoğunluğu **Cryptococcus neoformans**, daha nadiren **C. gattii**'dir
- SOT'ta özellikle MSS/dissemine tutulum açısından düşük eşik gerektirir
- 2024 global rehber: sendrom bazlı (menenjit / dissemine / pulmoner) yaklaşım; indüksiyon–konsolidasyon–idame konsepti.
- Klinik izlemin omurgası: BOS basıncı/klinik yanıt, ilaç toksisitesi, immünsüpresyon dengesi.
- Nüks/sekonder profilaksi kararları risk ve klinik yanıtla bireyselleştirilir.

Kriptokokkoz

2024 global rehber: sendrom bazlı (menenjit / dissemine / pulmoner) yaklaşım: **indüksiyon-konsolidasyon-idame konsepti:**

- İndüksiyon
  - Liposomal amphoterisin B 3-4 mg/kg
  - Flucytosine 25 mg/kg 4x1/ 2 hafta
- Konsolidasyon (8 hafta): Flukonazole 400-800 mg /gün
- İdame: Flukanazol 200 mg/gün, 12 ay

İlaç etkileşimleri, toksisite ve TDM

Transplant pratiğinde “kritik” bölüm

Azoller (vori/posa/itra)

CYP üzerinden takrolimus/siklosporin/mTOR düzeylerini ↑
→ nefrotoksisite, nörotoksisite, hipertansiyon
TDM + yakın düzey izlemi gerekir

Amfoterisin B (L-AmB)

Nefrotoksisite + elektrolit bozukluğu
CNI ile birlikte risk artar
Hidrasyon/elektrolit izlemi şart

Ekinokandinler

Etkileşim profili genelde daha “temiz”
Kandidemi/IC için sık başlangıç seçeneği
Odak/etken/PK ile uyum değerlendir

Antifungal başlamak = immünsüpresan dozunu ve düzey izlemini yeniden planlamak

Sonuç…

- SOT’da fungal enfeksiyonlar mortalite ve morbiditesi yüksek
- Antifungal yaklaşım **organ ve risk temelli olmalıdır**
- Epidemiyolojik veriler önemli
- İlaç etkileşimleri hayati önemdedir, TDM gerekli
- Multidisipliner yaklaşım şarttır


Doğru hasta
Doğru zaman
Doğru antifungal
Doğru strateji

Teşekkürler