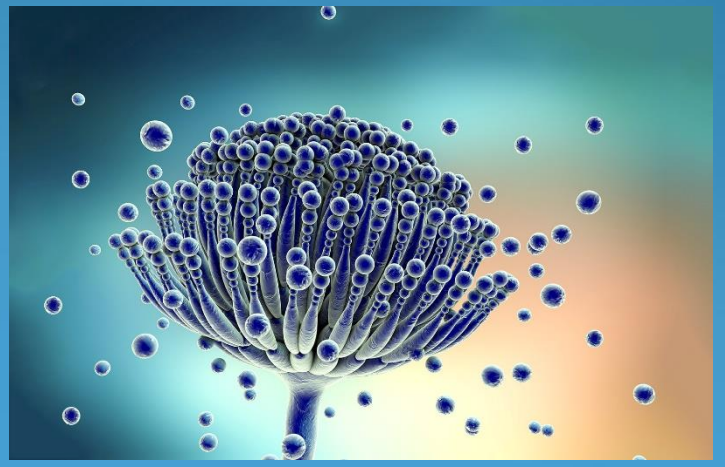
Transplant hastalarında İnvazif Fungal İnfeksiyonlar neden gelişiyor?

Dr.Hande Arslan

Başkent ÜTF



GODT

Global Observatory on Donation and Transplantation

WHO Collaborating Centre on Donation and Transplantation

GOBIERNO DE ESPAÑA MINISTERIO DE SANIDAD, POLITICA SOCIAL E IGUALDAD ONT

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 ...

126,670	5.8%	31,812	14.5
ORGANS TRANSPLANTED ANNUALLY (2015)	OF INCREASE OVER 2014	ACTUAL DECEASED ORGAN DONORS IN 2015	TRANSPLANTS/HOUR IN 2015

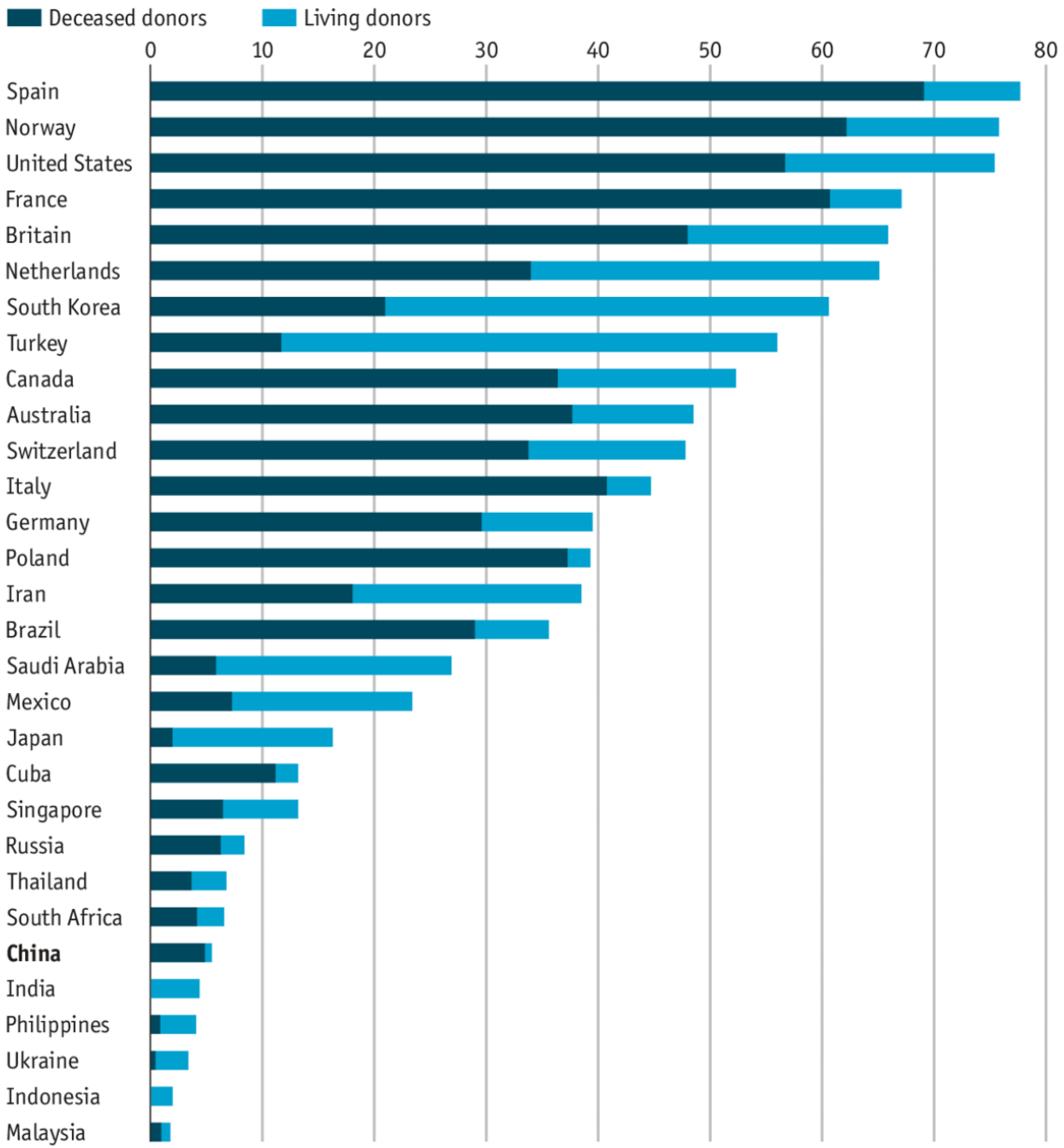
41.80% OF LIVING KIDNEY TRANSPLANTS (2015)

16.90% OF ACTUAL DCD (2015)

21% OF LIVING LIVER TRANSPLANTS (2015)

Transplants* per million people

Selected countries, 2013 or latest



Sources: Global Observatory on Donation & Transplantation; WHO; ONT

*Kidney and liver transplants, which comprised almost 90% of all transplants in 2012

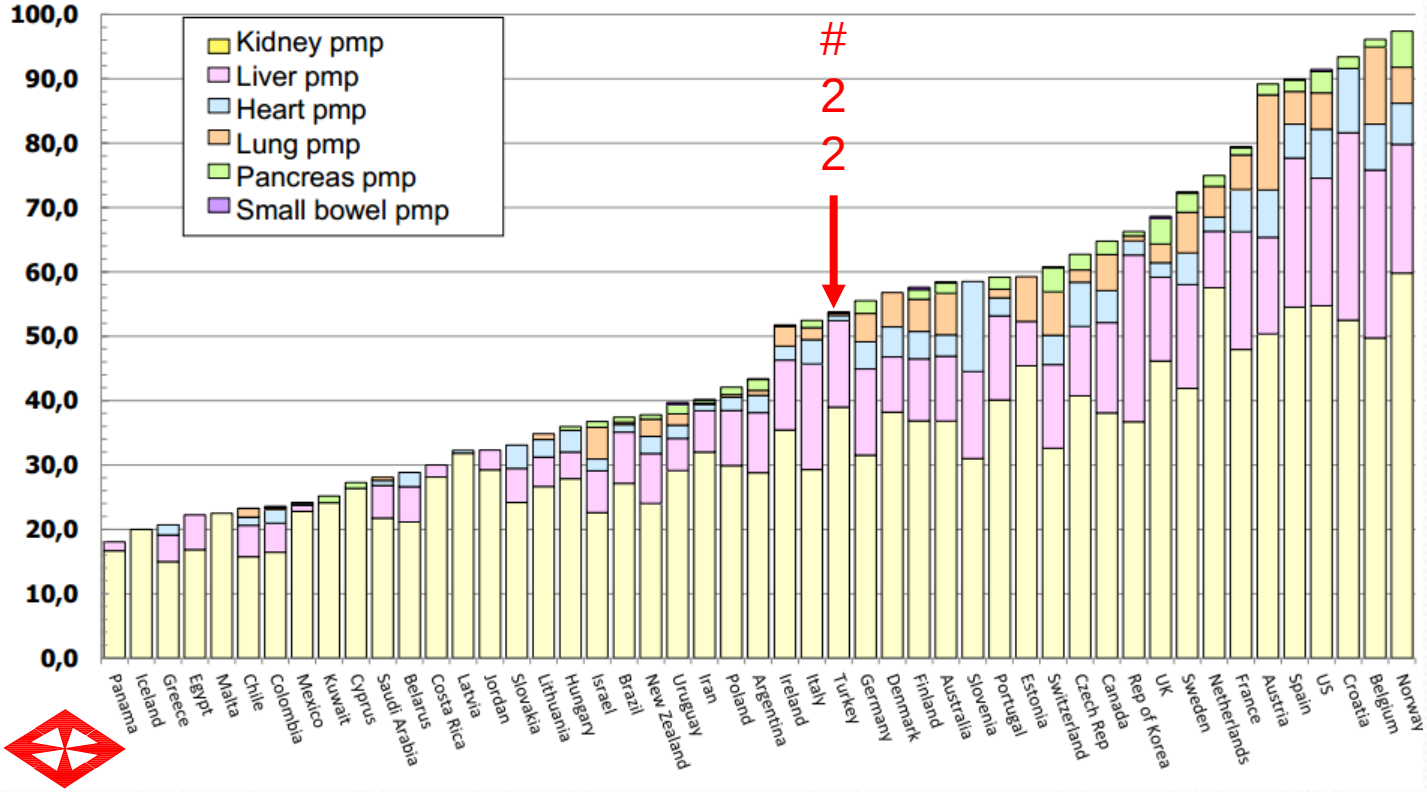
Economist.com/graphicdetail

GODT Global Observatory on Donation & Transplantation

In collaboration with World Health Organization

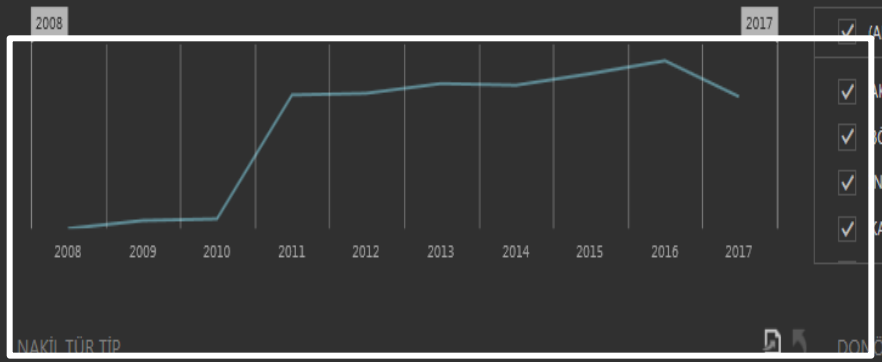
ONT World Health Organization GODT 2012

Transplanted Organs per Million Population
50 Most Active Countries Globally

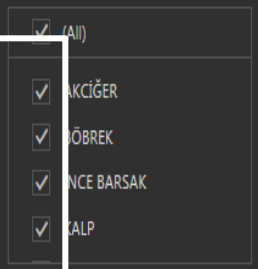


ORGAN NAKLİ SAYILARI

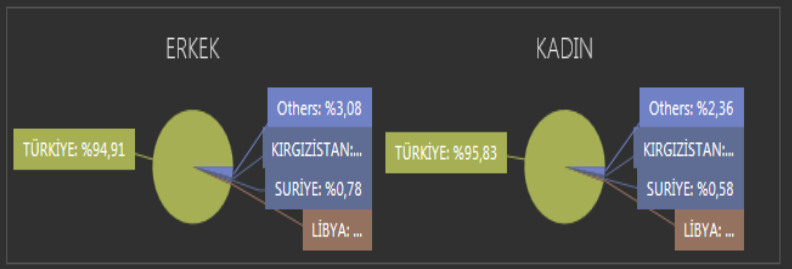
TARİH ARALIĞI



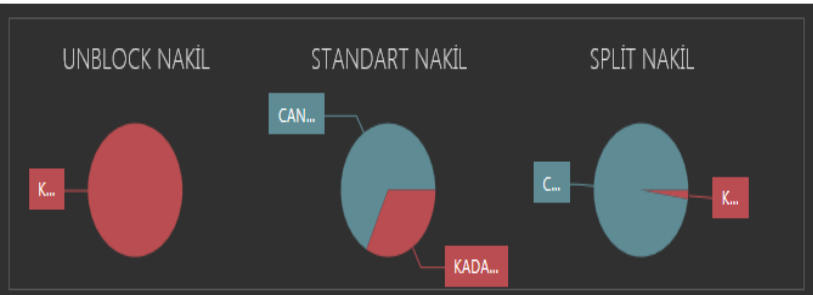
ORGAN



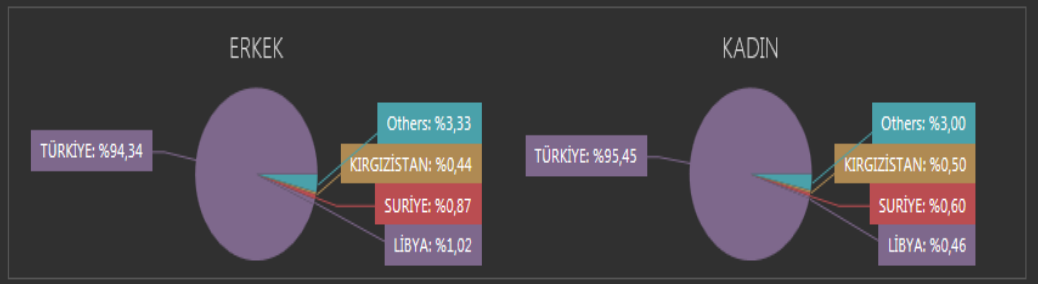
HASTA DAĞILIMI



NAKİL TÜR TİP



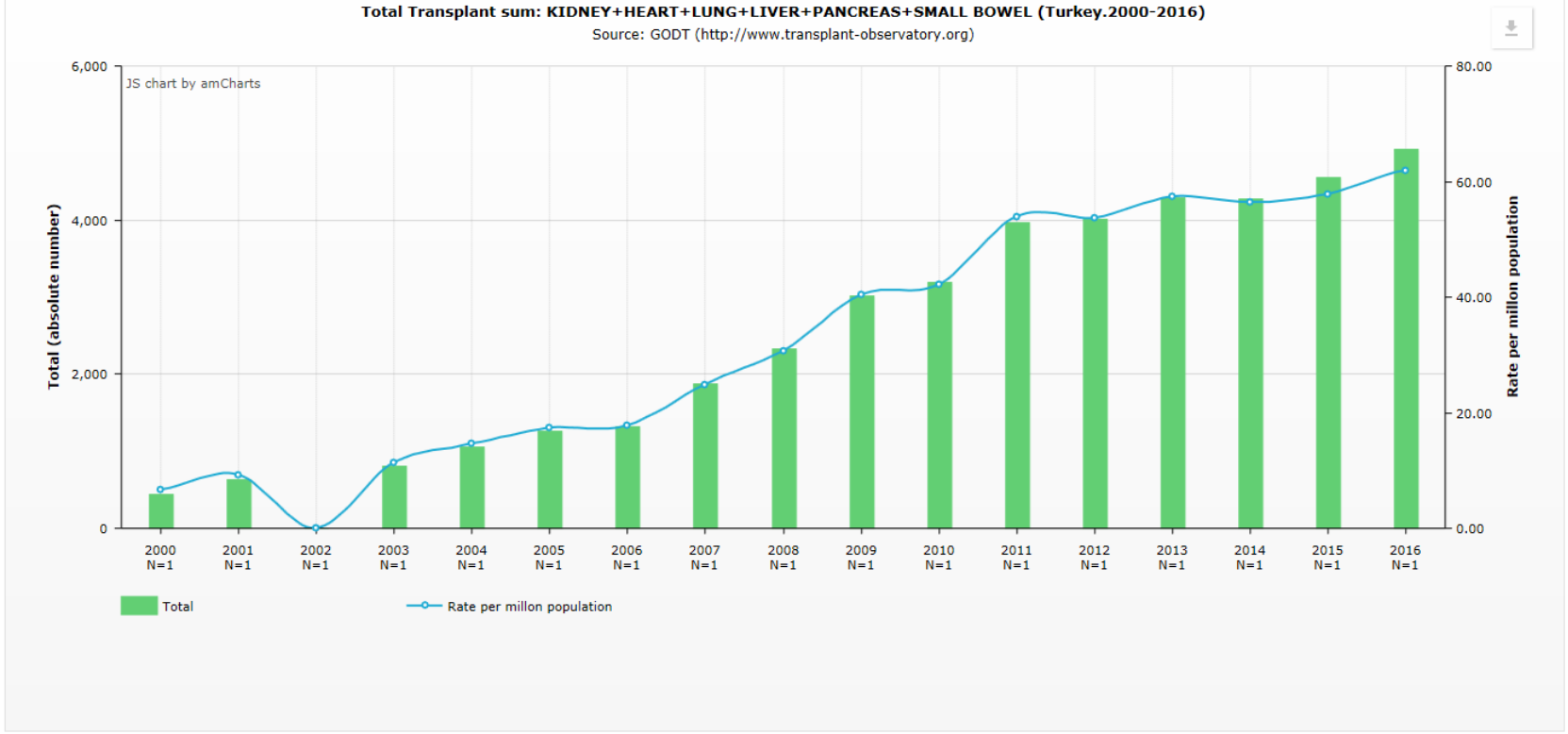
DONÖR DAĞILIMI



ÖZET BİLGİ

	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	Grand Total
AKCİĞER	34	22	30	33	32	25	5				181
BÖBREK	2.690	3.423	3.204	2.925	2.946	2.909	2.952	471	413	6	22.139
İNCE BARSAK	2	5	6	5	2	5	2				27
KALP	62	69	89	78	63	61	95				517
KALP KAPAĞI				2	1	5	1				9
KARACİĞER	1.154	1.397	1.218	1.212	1.249	1.002	908	17	4		8.161

Türkiye- SOT Olguları



http://www.transplant-observatory.org/data-charts-and-tables/chart/

SOT alıcılarında

- Transplantasyon sonrası infeksiyöz komplikasyonlar hala yüksek

- ***İnvazif fungal infeksiyonlar*** hastaların genel durumunun hızla bozulmasına ve yüksek mortalite gelişmesine neden olur

3N1H

- Ne sıklıkta?
- Ne zaman?
- Neden ?
- Hangi transplantasyonda?

Ne sıklıkta?

- SOT hastalarında İFİ yükünü tespit etmek zor

- Bununla birlikte;
  - İlk bir yıldaki kümülatif insidans %3 (***Pappas PG CID 2010***)
  - Mortalite;
    - %27-30 (en sık karaciğer tx.) (***Neofytos D transpl Infect Dis 2010***)
  - Maliyet;
    - 23.5 gün uzamış hastane yatışı
    - 62,697 dolar ekstra harcama (***Menzin J Am J Infect Control 2011***)
  - Candida + Aspergillus >% 80

Hangi transplantasyon tipinde daha çok?

Transplant International ISSN 0934-0874
2007

REVIEW

Invasive fungal infections and antifungal therapies in solid organ transplant recipients

Steven Gabardi,[1,2,3] David W. Kubiak,[1,4] Anil K. Chandraker[2,3] and Stefan G. Tullius[3,5]

1 Department of Pharmacy Services, Brigham and Women's Hospital, Boston, MA, USA
2 Renal Division, Brigham and Women's Hospital, Boston, MA, USA
3 Harvard Medical School, Boston, MA, USA
4 Infectious Disease Division, Brigham and Women's Hospital, Boston, MA, USA
5 Department of Renal Transplant Surgery, Brigham and Women's Hospital, Boston, MA, USA

Table 1. Incidence of invasive fungal infections among transplant recipients [1–3,33,121].

Type of transplant	Incidence of IFIs (%)	Usual etiologic pathogen(s)
Heart	3–21	70–90% *Aspergillus*
Liver	4–42	35–91% *Candida* 9–34% *Aspergillus*
Lung and heart/lung	10–44	43–72% *Candida* 25–50% *Aspergillus*
Pancreas	6–38	97–100% *Candida*
Renal	1–14	50–80% *Candida* 7–19% *Aspergillus*
Small bowel	40–59	90% *Candida*

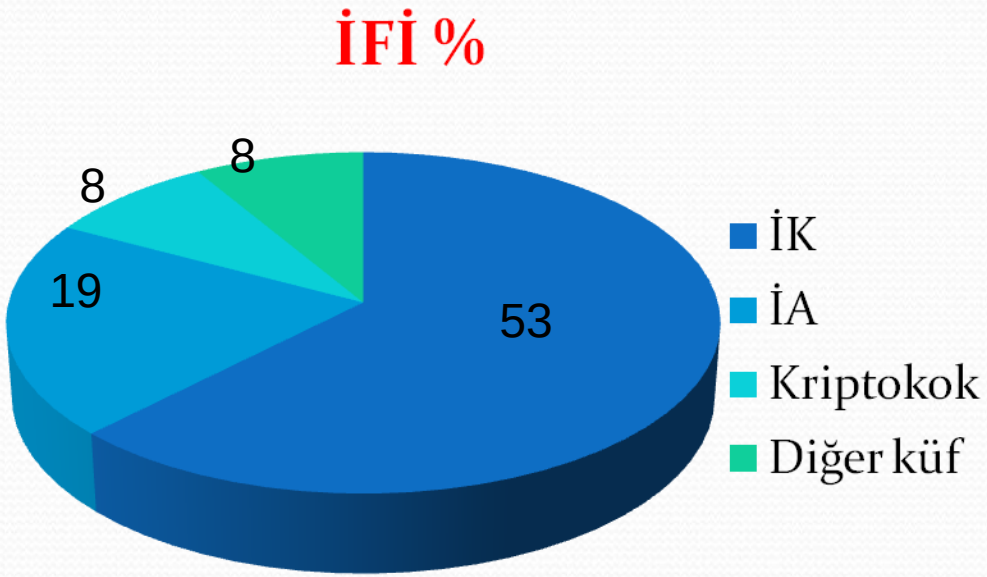
MAJOR ARTICLE

Clinical Infectious Diseases 2010;50:1101–1111

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]

23 transplantasyon merkezi
5 yıl
1063 organ alıcısı
1208 İFİ
Kümülatif insidans %3.1



Distribution of 515 invasive fungal infections (IFIs) among 429 solid organ transplant recipients

IFI[1]	Overall *N* = 515 (%)	Liver *N* = 127 (%)	Lung *N* = 134 (%)	Kidney *N* = 109 (%)	Heart *N* = 40 (%)	Kidney–pancreas *N* = 38 (%)	Kidney–live *N* = 25 (%)
Candida species[2]	304 (59.0)	100 (78.7)	32 (23.9)	66 (60.6)	26 (65.0)	29 (76.3)	21 (84.0)
Candida albicans	141 (46.4)	45 (45.0)	21 (65.6)	33 (50.0)	12 (46.2)	16 (55.2)	5 (23.8)
Candida glabrata	113 (37.2)	41 (41.0)	7 (21.9)	20 (30.3)	6 (23.1)	11 (37.9)	9 (42.9)
Candida krusei	14 (4.6)	4 (4.0)	0	3 (4.5)	1 (3.8)	0	5 (23.8)
Candida parapsilosis	19 (6.3)	5 (5.0)	3 (9.4)	6 (9.1)	4 (15.4)	1 (3.4)	0
Candida tropicalis	11 (3.6)	2 (2.0)	1 (3.1)	4 (6.1)	1 (3.8)	1 (3.4)	2 (9.5)
Aspergillus species	128 (24.8)	10 (7.9)	80 (63.0)	13 (11.9)	10 (25.0)	4 (10.5)	2 (8.0)
Aspergillus flavus	13 (10.2)	0	6 (7.5)	1 (7.7)	2 (20.0)	1 (25.0)	0
Aspergillus fumigatus	79 (61.7)	6 (60.0)	50 (62.5)	11 (84.6)	4 (40.0)	2 (50.0)	0
Aspergillus niger	13 (10.2)	0	11 (13.7)	0	0	1 (25.0)	1 (50.0)
Aspergillus terreus	4 (3.1)	0	4 (5.0)	0	0	0	0
Other	10 (7.8)	2 (20.0)	6 (7.5)	1 (7.7)	1 (10.0)	0	0
Unknown	9 (7.0)	2 (20.0)	3 (3.7)	0	3 (30.0)	0	1 (50.0)
Cryptococcus species	36 (7.0)	9 (7.1)	3 (2.2)	21 (19.3)	1 (2.5)	0	1 (4.0)
Zygomycetes[3]	10 (1.9)	4 (3.1)	3 (2.2)	1 (0.9)	1 (2.5)	0	0
Rhizopus	7 (70.0)	3 (75.0)	2 (66.7)	1 (100.0)	1 (100.0)	0	0
Endemic fungi[4]	10 (1.9)	1 (0.8)	2 (1.5)	4 (3.7)	1 (2.5)	2 (5.3)	0
Histoplasma species	6 (60.0)	1 (100.0)	0	3 (75.0)	0	2 (100.0)	0
Other yeast[5]	7 (1.4)	3 (2.4)	1 (0.7)	1 (0.9)	0	1 (2.6)	1 (4.0)
Other molds[6]	20 (3.9)	0	13 (9.7)	3 (2.7)	1 (2.5)	2 (5.3)	0
Fusarium species	3 (15.0)	0	3 (23.0)	0	0	0	0
Scedosporium apiospermum	5 (25.0)	0	5 (38.5)	0	0	0	0

Transplante edilen organ tipi

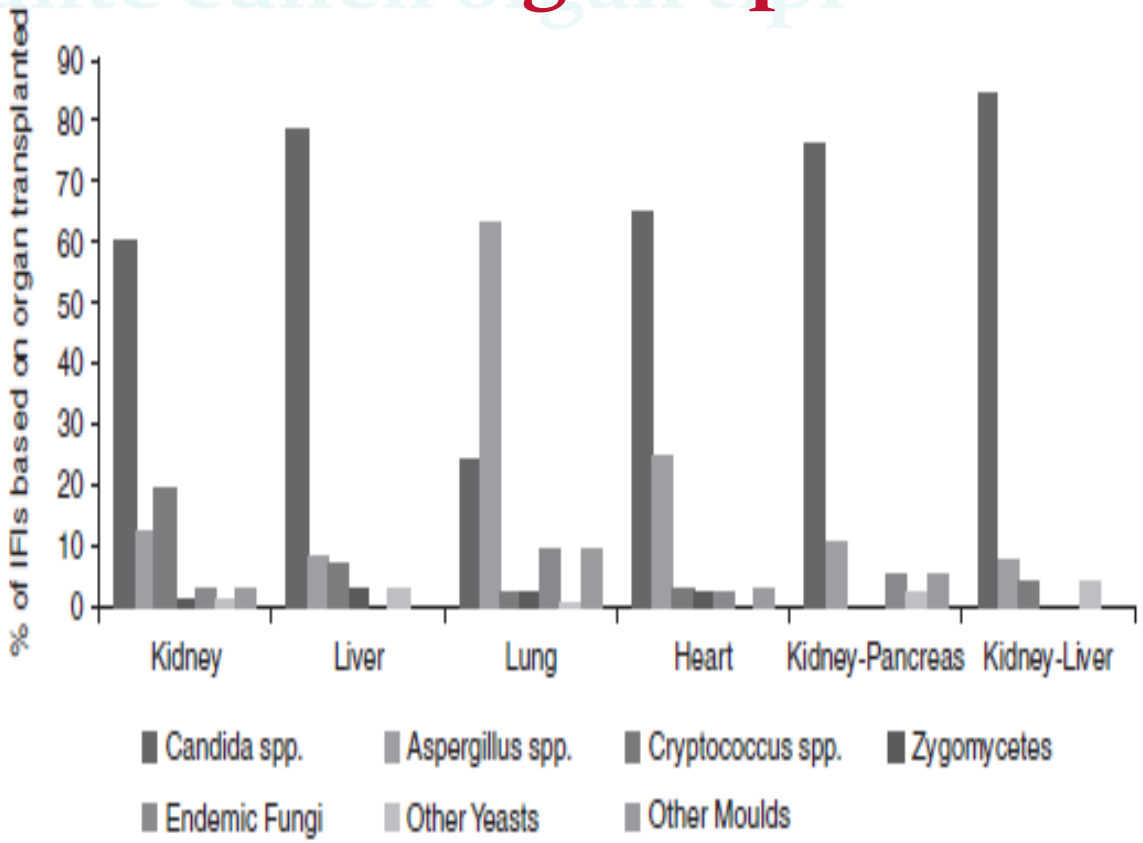
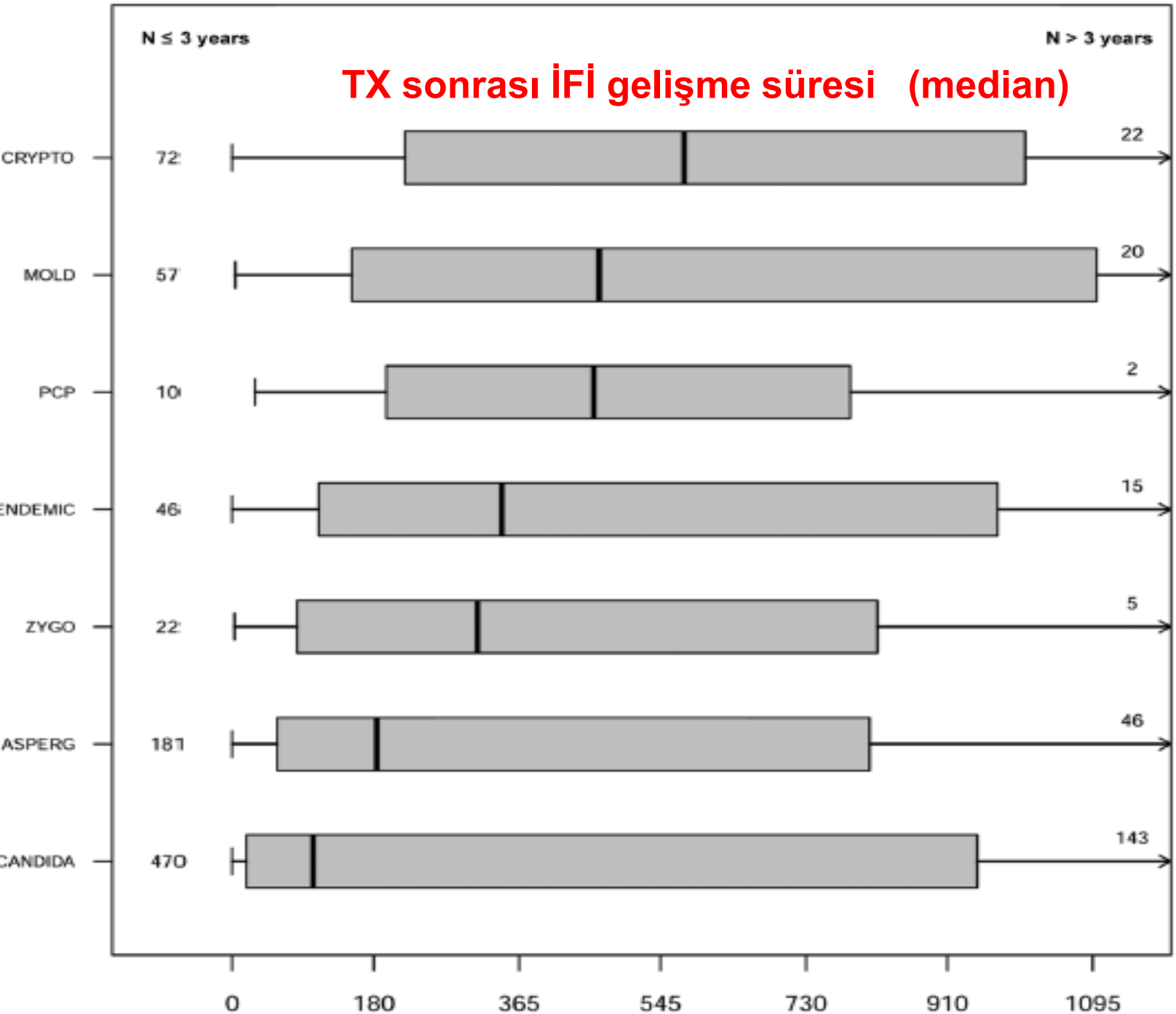
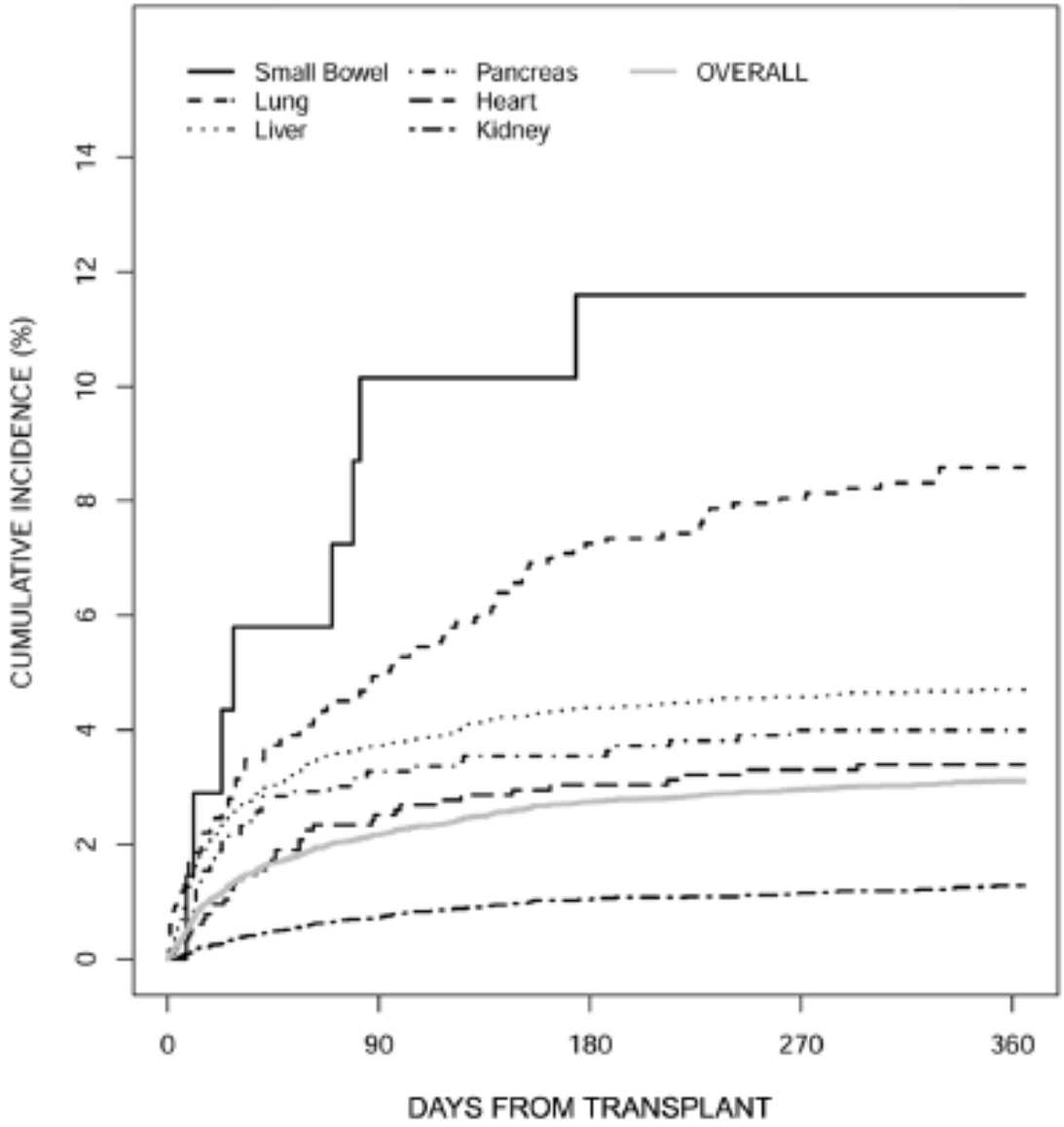


Fig. 1. Distribution of invasive fungal infections (IFIs) among the most common solid organ transplant categories. spp., species.

Ne zaman?


N ≤ 3 years
N > 3 years
TX sonrası İFİ gelişme süresi (median)
CRYPTO
72
22
MOLD
57
20
PCP
10
2
ENDEMIC
46
15
ZYGO
22
5
ASPERG
181
46
CANDIDA
470
143
0
180
365
545
730
910
1095



İlk İFİ'un görülme insidans körvü

Neden?

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

doi: 10.1111/ajt.13186

Minireview

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

Farmakiotis and Kontoyiannis

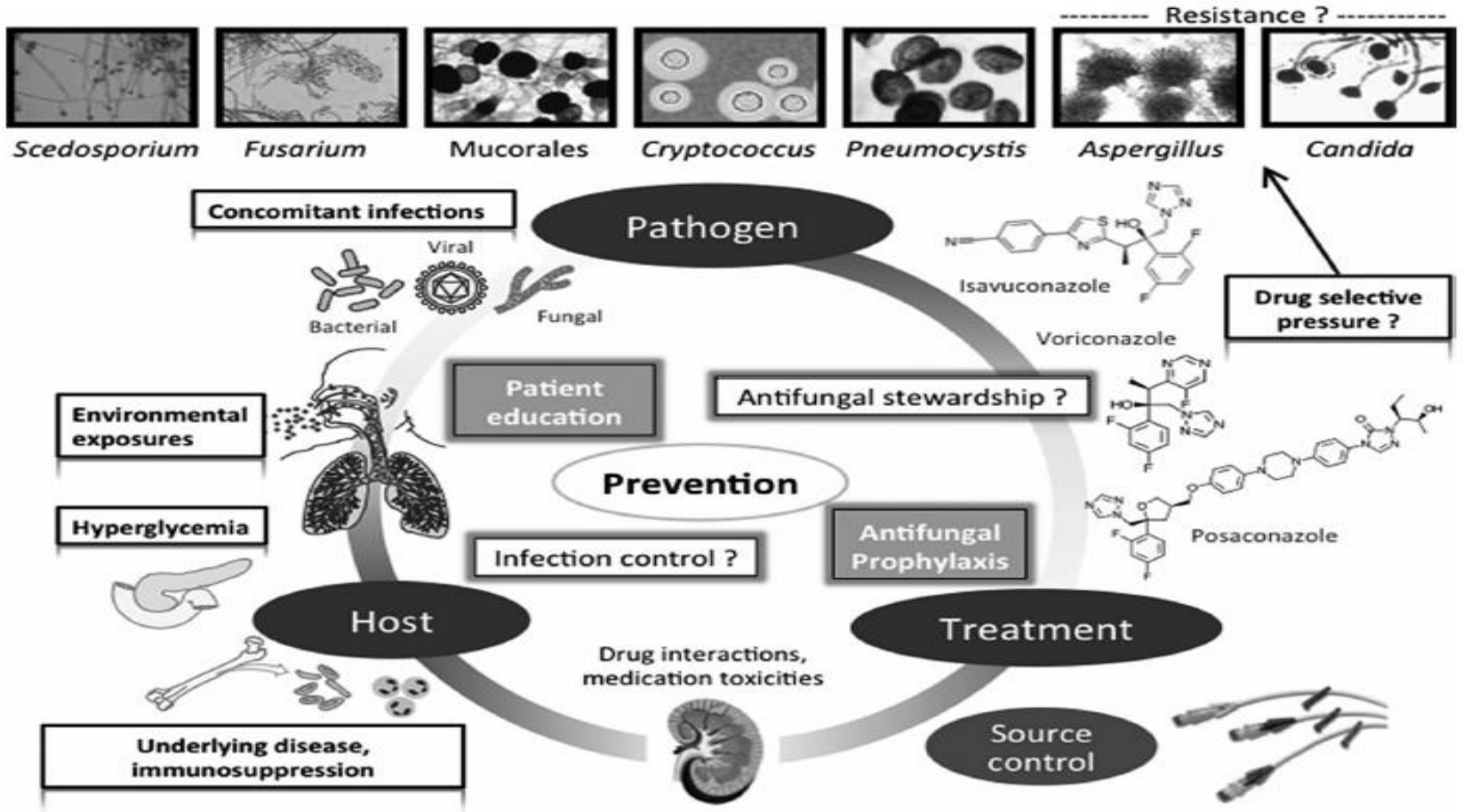


Figure 1: Factors influencing the pathogenesis, prevention, and treatment of emerging fungal infections in solid organ transplant recipients.

İFİ gelişimi için ortak risk faktörleri

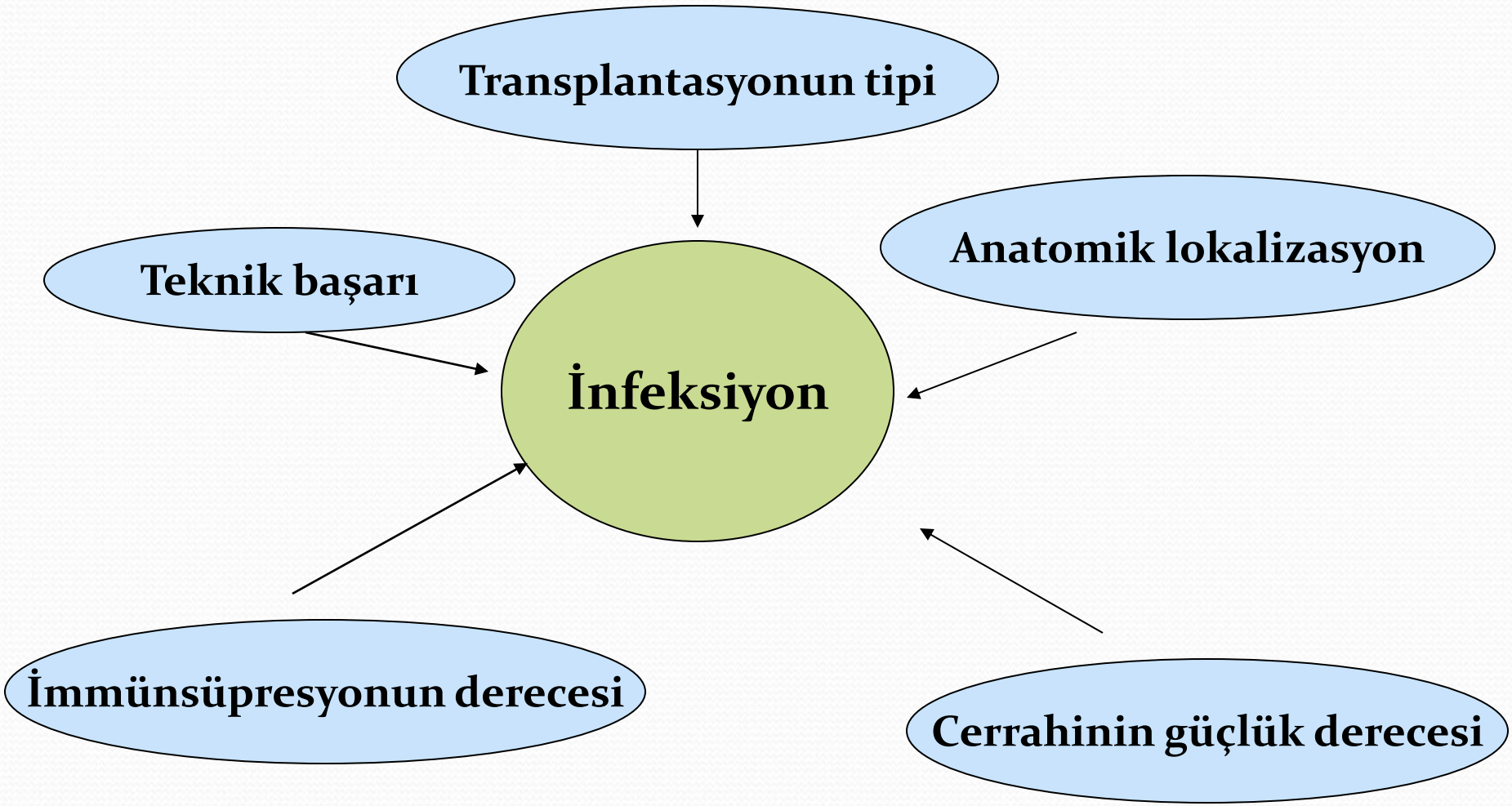
Cerrahi faktörler;

- Transplantasyon türü
- Teknik ve anatomik komplikasyonlar

İmmünsüpresyonun derecesi

Epidemiyolojik temas

Cerrahi teknik ve anatomik komplikasyonlar



Epidemiyolojik temas

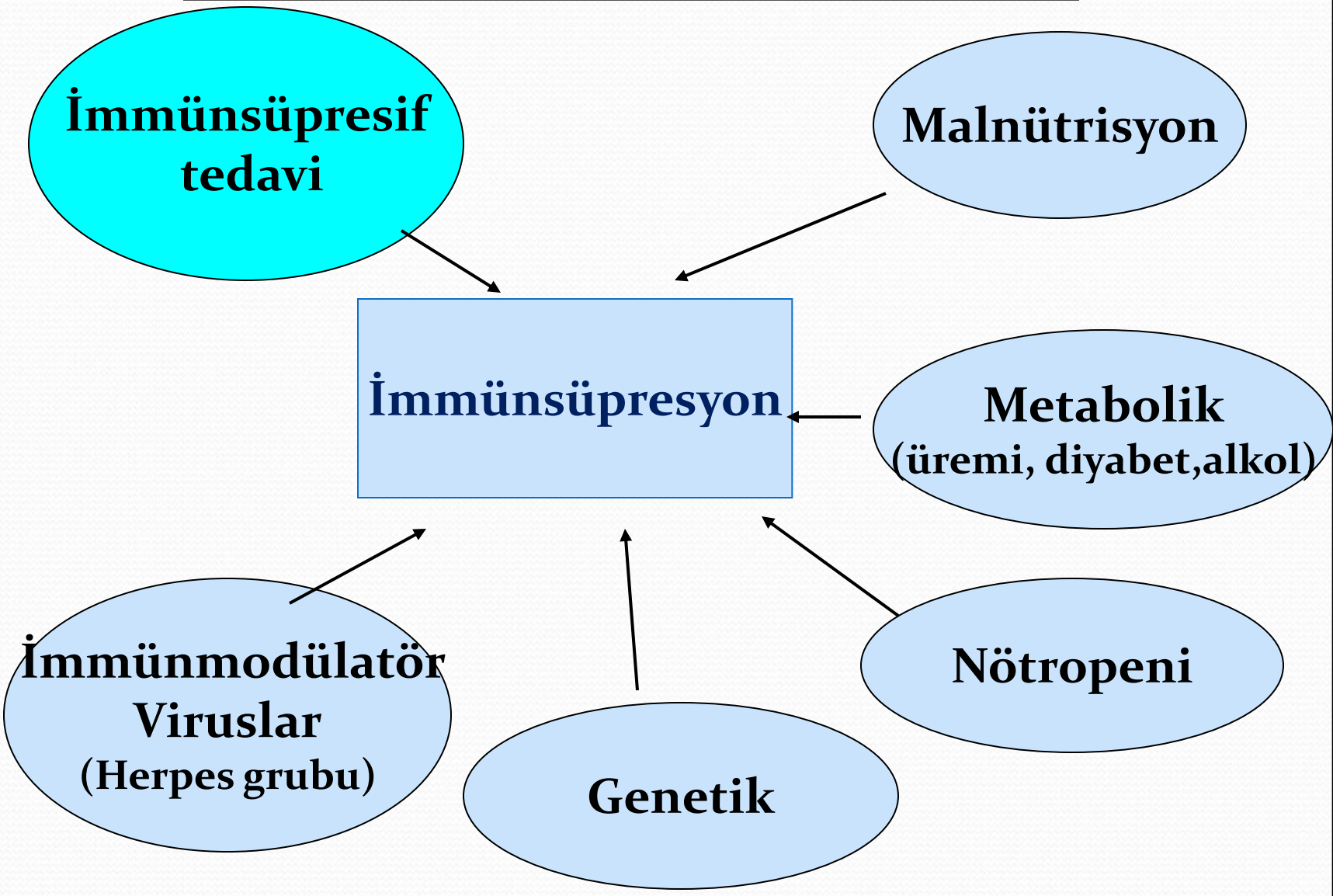
Toplumsal temas

Mesleki, tarımsal temaslar
Rekonstrüksiyon çalışmaları
Endemik alana yolculuk

Nozokomiyal temas

Rekonstrüksiyon çalışmaları
Kontamine su
Havalandırma
Uzun Yoğun Bakım kalışı
Uzamış mekanik ventilasyon
El yıkama zafiyeti

İmmünsüpresyonun net durumu



REVIEW 10.1111/1469-0691.12660

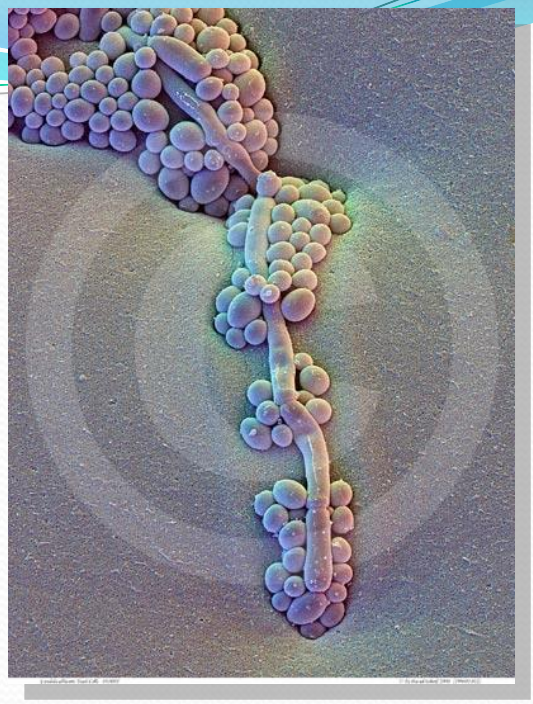
Invasive fungal infections in solid organ transplant recipients

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)

1) Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Barcelona, 2) Infectious Diseases Department, Hospital Universitario Ramón y Cajal, Madrid,Spain, 3) Infectious Diseases Unit, 3rd Department of Pediatrics, Faculty of Medicine, Aristotle University School of Health Sciences and Hippokration General Hospital, Thessaloniki, Greece, 4) AP-HP, Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif , 5) Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants Malades, Centre d'Infectiologie Necker-Pasteur, IHU Imagine and Centre National de Référence Mycoses Invasives et Antifongiques, Unité de Mycologie Moléculaire, Institut Pasteur, Université Paris Descartes, CNRS URA3012, Paris, France, 6) Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, 7) Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, 8) CIBER Enfermedades Respiratorias-CIBERES (CB06/06/0058), Madrid, 9) Medicine Department, School of Medicine, Universidad Complutense de Madrid, Madrid, 10) Infectious Diseases Section, Department of Surgical and Morphological Sciences, University of Insubria, Varese, Italy and 11) Micology Service, Centro Nacional de Microbiología, Madrid, Spain

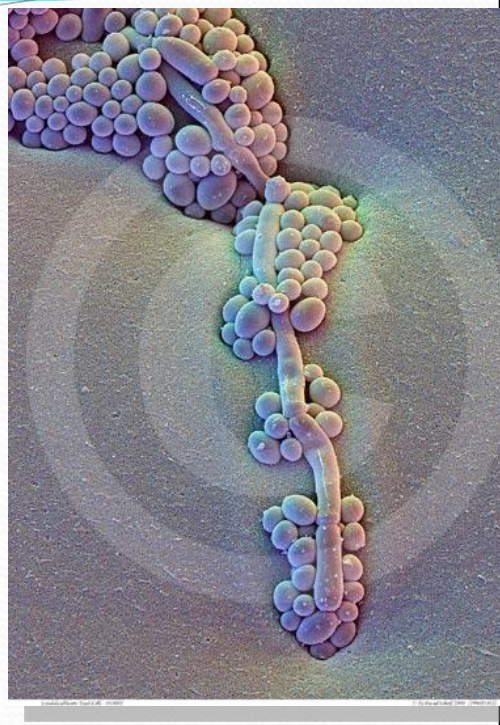
Clin Microbiol Infect 2014; **20** (Suppl. 7): 27–48

İnvazif Kandidiyazis (İK) için risk faktörleri;



- En çok erken post transplantasyon dönemde
  - gastrointestinal sistem
  - vasküler kateter
  - graft kaynaklı

Karaciğer (İK)



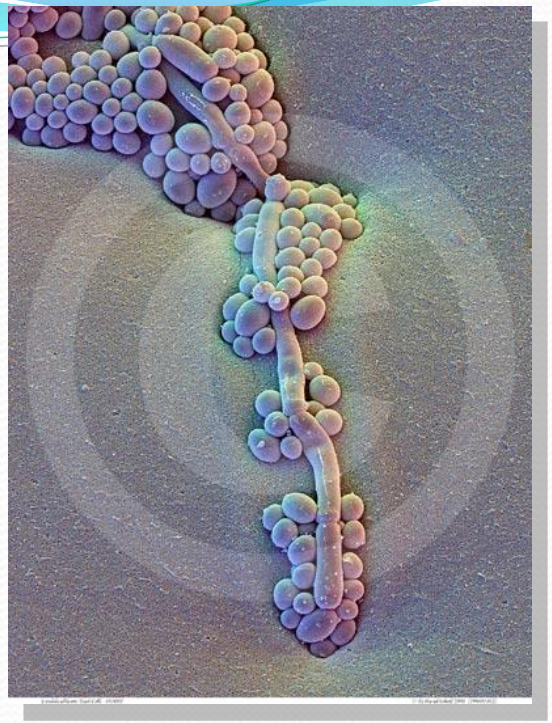
Majör risk faktörleri;

- MELD Skoru>30
- Re-transplantasyon
- Fulminan hepatik yetmezlik
- Replasman tedavisi gerektiren renal yetmezlik

Minör Risk Faktörleri

- MELD skoru 20-30, split karaciğer (canlıdan)
- >40 ünite kan ürünü transfüzyonu
- Koledokojejunostomi (Roux-enY)
- Replasman tedavisi gerektirmeyen renal yetmezlik Kr KL<%50
- Erken dönemde girişimsel işlem, multifokal kolonizasyon/ infeksiyon

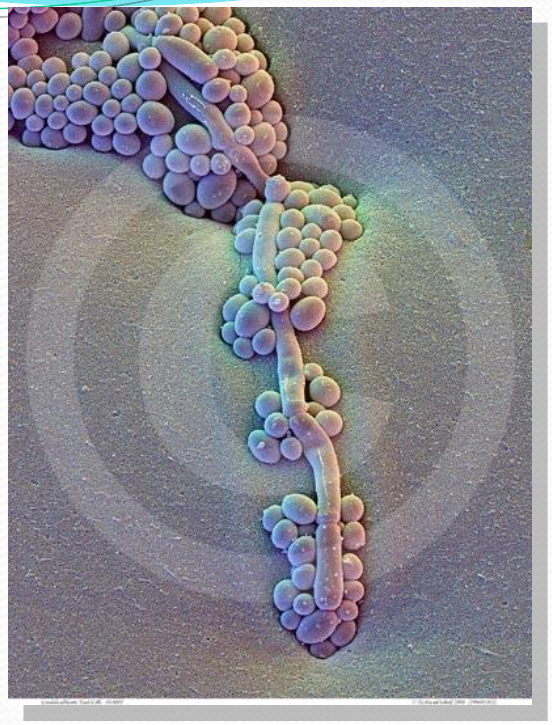
Barsak

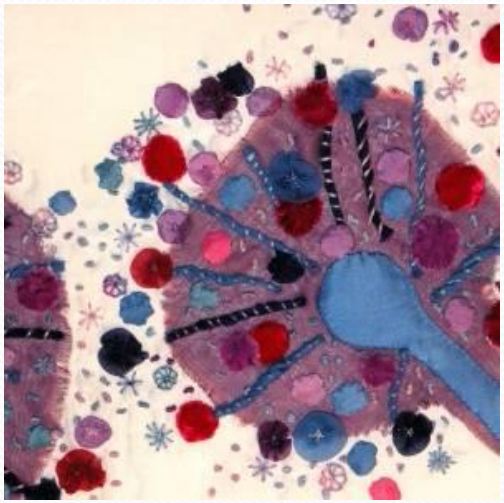


- Akut Rejeksiyon
  - Başlangıçta zayıf allograft fonksiyonu
  - Anastomatik problemler
  - Hemodiyaliz
  - Tx sonrası Laporotomi
  - Yüksek imünsüprsyon

Kalp:

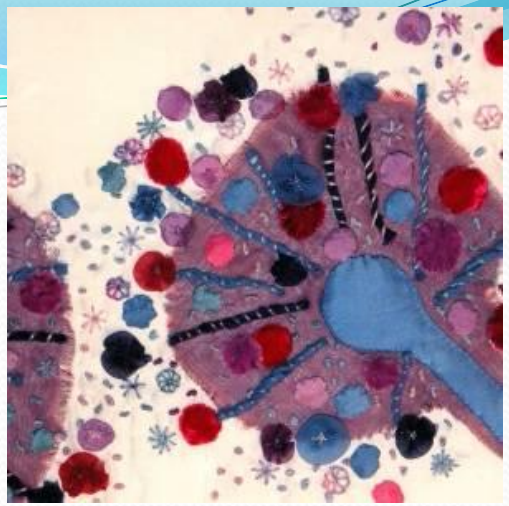
- Akut rejeksiyon
- Hemodiyaliz
- Tx sonrası reeksplorasyon





İnvazif Aspergillosiz için risk faktörleri;

Karaciğer



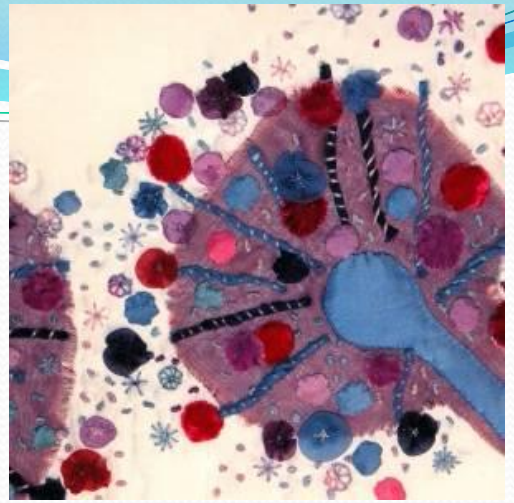
Erken Dönem İA

- Re-transplantasyon
- Post tx böbrek yetmezliği
- Hemodiyaliz
- Fulminan Hepatik Yetmezlik
- Komplike cerrahi
- Reoperasyon

Geç Dönem İA>3 ay

- Son üç ay içinde 6 gramın üzerinde kümülatif prednison
- Post-tx renal yetmezlik
- Post tx hemodiyaliz
- Lökopeni <500/mm3
- Kronik graft disfonksiyonu

Akciğer



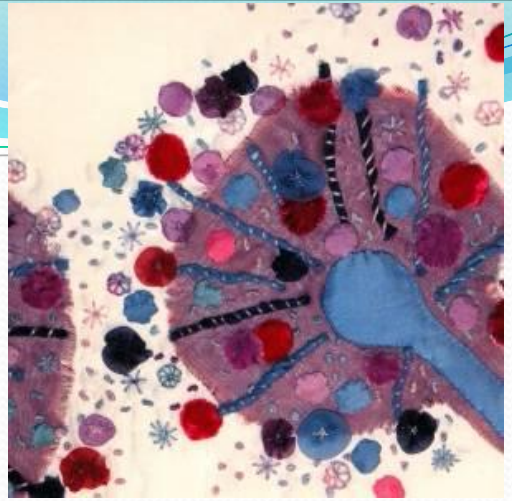
Erken Dönem İA

- Bronkial anastomotik iskemi
- Bronkial stent
- Akut rejeksiyon
- Tek akciğer tz
- Tx öncesi ve posttx ilk yıl aspergillus kolonizasyonu

Geç Dönem İA (>3 ay)

- Kronik graft disfonksiyonu

Kalp



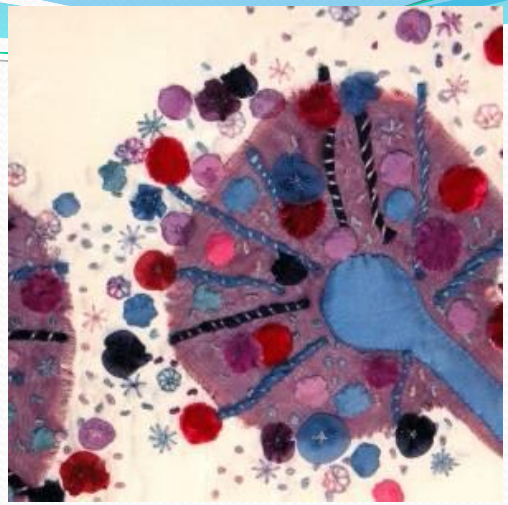
Erken Dönem İA

- Akut rejeksiyon
- Solunum yollarının aspergillus kolonizasyonu
- Re-operasyon
- Hipogammaglobülinemi(Ig<400mg/dl)
- Post tx hemodiyaliz

Geç Dönem İA (>3 ay)

- YBÜ ye yeniden girmek
- Böbrek transplantasyonu
- >2 akut rejeksiyon atağı geçirmek

Böbrek



Erken Dönem İA

- Graft kaybı nedeniyle hemodiyaliz
- Tx sonrası Hemodiyaliz
- Uzamış yüksek steroid kullanımı
- CMV enfeksiyonu
- Yüksek immünsüpresyon

İnvazif Kriptokokkoziz için risk faktörleri;

- Geç dönem (16-21 ay)
- Yüksek doz kortikosteroid
- Alemtuzumab ve inflixumab kullanımı
- Kuş ve yarasa çıktılarıyla temas

Neden?

Transplantasyonun başarısı

- Uygun organ sağlanması
- Başarılı cerrahi teknik
- **Başarılı selektif immünosüpresyon**
- Transplantasyon sonrası bakım

Curr Fungal Infect Rep (2017) 11:148–157
DOI 10.1007/s12281-017-0278-5

FUNGAL GENOMICS AND PATHOGENESIS (S SHOHAM, SECTION EDITOR))

Pathogenesis of Invasive Pulmonary Aspergillosis in Transplant Recipients

Palash Samanta[1] · M. Hong Nguyen[1,2]

FEMS Microbiology Reviews, fuv018, 39, 2015, 670–687

doi: 10.1093/femsre/fuv018
Advance Access Publication Date: 1 May 2015
Review Article

REVIEW ARTICLE

The innate immune response to *Aspergillus fumigatus* at the alveolar surface

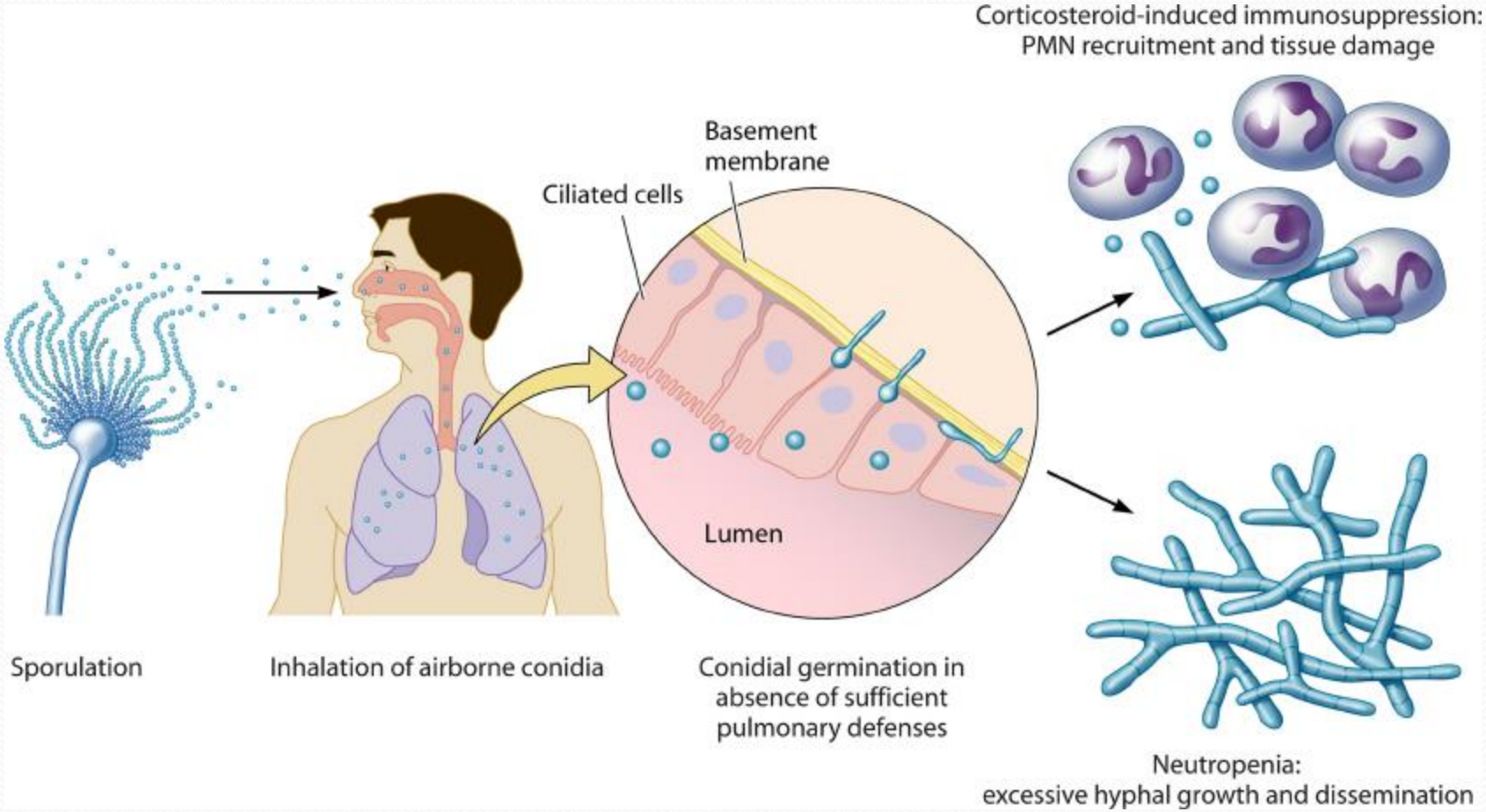
Anatte Margalit and Kevin Kavanagh*

Department of Biology, Maynooth University, Co. Kildare, Ireland

- İmmünsistemdeki dengesizlik patojen hale geçmesine neden oluyor

3 formda hastalık yapıyor;

- Sabrofitik aspergillozAspergilloma (normal veya hiper immünyanıt)
- Allerjik aspergilloz Allerjik Bronko Pulmoner Aspergilloz (hiperimmünyanıt)
- İnvazif Fungal Aspergilloz (immünyetmezlik)


Corticosteroid-induced immunosuppression:
PMN recruitment and tissue damage
Basement membrane
Ciliated cells
Lumen
Sporulation
Inhalation of airborne conidia
Conidial germination in absence of sufficient pulmonary defenses
Neutropenia:
excessive hyphal growth and dissemination

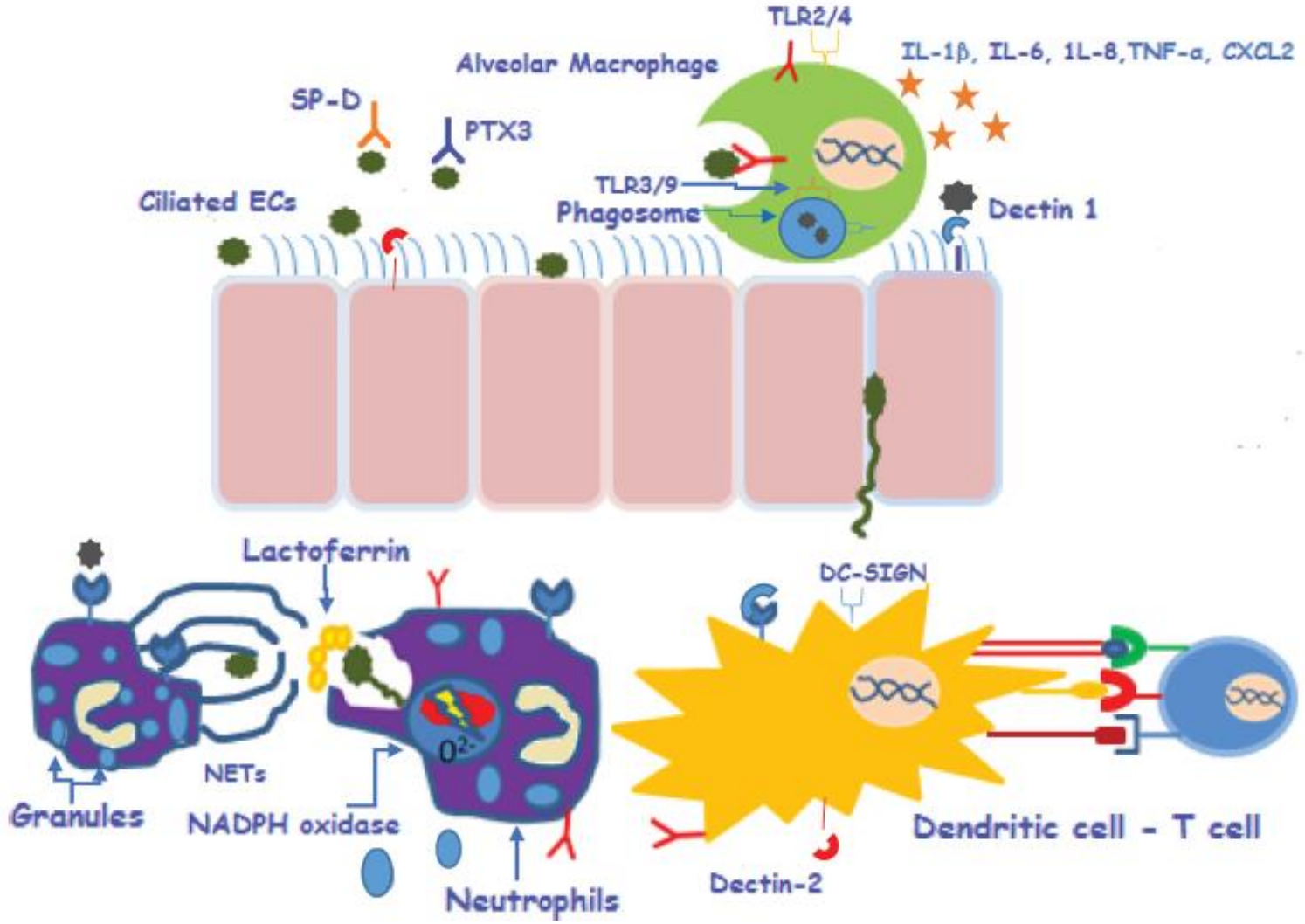
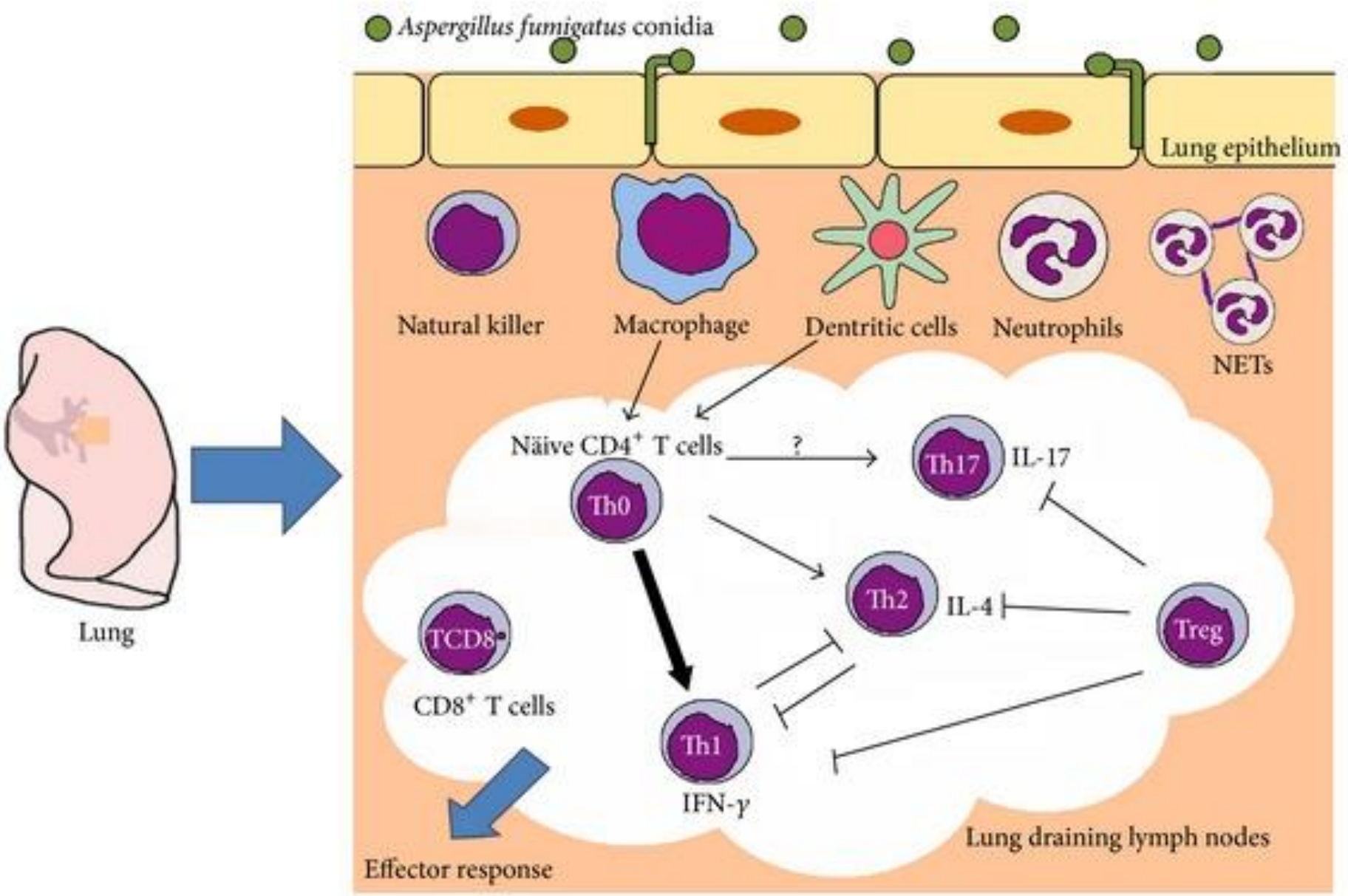
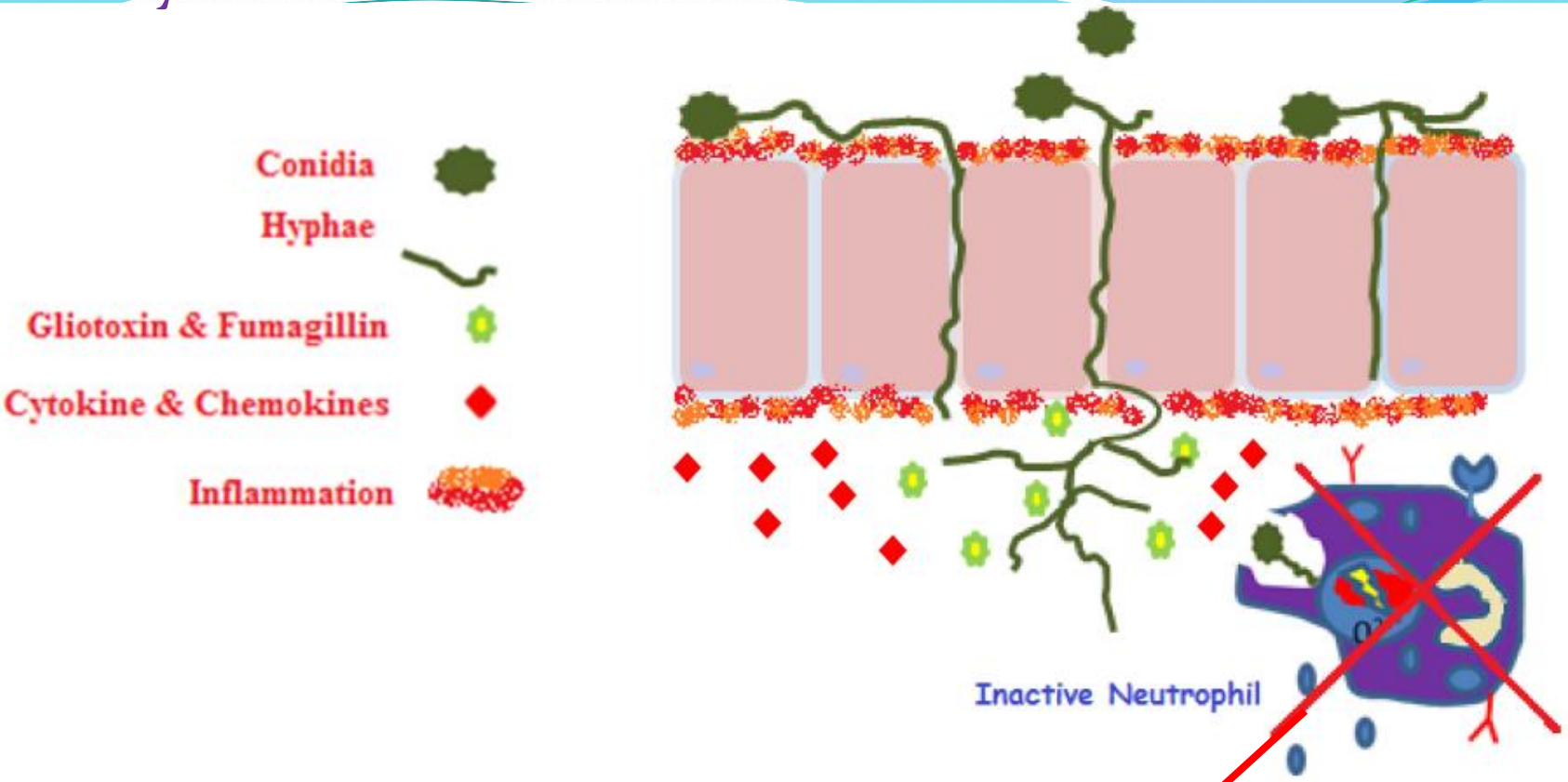


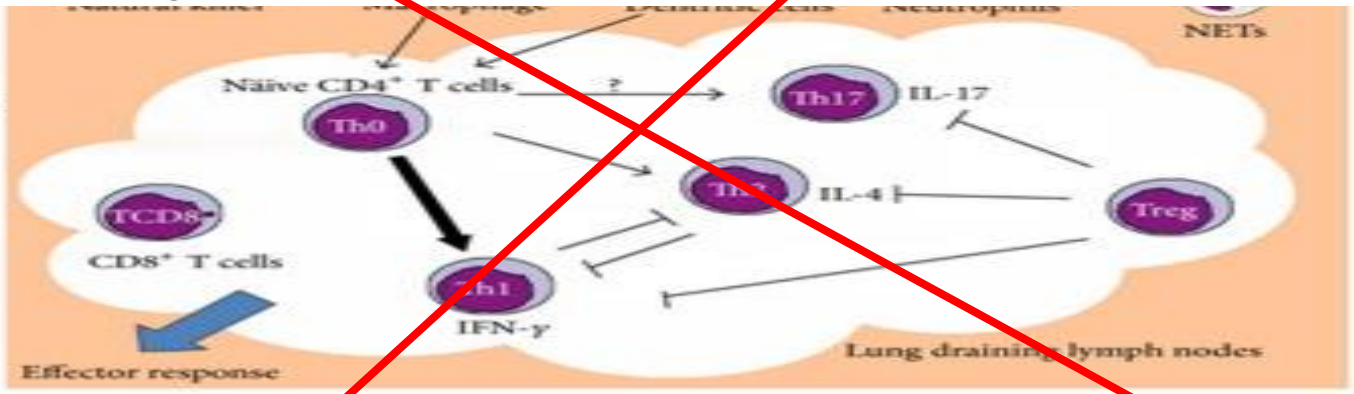
Figure 4. In the immunocompetent lung, conidia are immediately met by a host of soluble recognition receptors including PTX3 and SP-D which bind to and enhance conidial phagocytosis by AM. AM recognition and uptake of conidia is mediated by Dectin-1 and TLRs and leads to the induction of a proinflammatory response. Conidia that have escaped attack by AM, germinate and penetrate through the alveolar surface. AM- and EC-derived proinflammatory mediators recruit neutrophils to the site of infection. Neutrophils employ oxidative-dependent (ROS generation) and oxidative-independent (NET formation, degranulation and lactoferrin production) mechanisms to inactivate germinating conidia and hyphae. At the site of infection, DCs phagocytose and process germinated conidia for subsequent antigen presentation to naïve T cells which in turn activate an adaptive immune response to *A. fumigatus*.


Aspergillus fumigatus conidia
Lung epithelium
Natural killer
Macrophage
Dentritic cells
Neutrophils
NETs
Lung
Näive CD4+ T cells
?
Th17
IL-17
Th0
Th2
IL-4
Treg
TCD8
CD8+ T cells
Th1
IFN-γ
Lung draining lymph nodes
Effector response

İmmünyetmezlikli Hastada



host may experience invasive hyphal growth which can disseminate through the epithelial and endothelial cell mem-
ited immune response.



- Fırsatçı funguslarda patogenez neden önemli?
  - Klinik
  - Tedavi

KLİNİK

Table 2 Classification of clinical manifestations of aspergillosis according to damage response framework

Aspergillus colonization				
Host response	Severe immunosuppression	Non-neutropenic, chronic steroid administration +/– other immunosuppression	Normal immunity to mild immunosuppression, with broncho-pulmonary disorders[a]	Hyperactive immunity
Examples of clinical scenerios	Neutropenia Acute leukemia HSCT	Solid organ transplant	Cavitary lung disease Bronchiectasis Cystic fibrosis	- Asthma - Exposure to *Aspergillus*
Histopathology and host damage	- High fungal burden, angioinvasion, intra-alveolar hemorrhage - Severe tissue destruction	- Few hyphae and conidia, neutrophilic and monocytic infiltrates - Areas of pneumonia and bronchiolitis	Colonization	- Allergic - Chronic immune activation
Examples of clinical entities	- IPA - ITBA, pseudomembranous	- IPA - ATB, - ITBA, ulcerative	- Aspergilloma - Airway colonization	- ABPA - ? BOS
Treatment	Antifungal Surgical resection	Antifungal Surgical resection	None if asymptomatic	Steroid and antifungal

[a] Patients with pre-existing pulmonary cavities, cystic fibrosis, and other bronchopulmonary disorders like chronic obstructive pulmonary diseases and bronchiectasis are prone to *Aspergillus* colonization. However, these conditions alone are not sufficient to cause IPA, unless there is an epithelial damage or the patient receives immunosuppressive therapy

Transplant Infectious Disease. ISSN 1398-2273

Clinical and radiological features of invasive pulmonary aspergillosis in transplant recipients and neutropenic patients

S.Y. Park, S.-H. Kim, S.-H. Choi, H. Sung, M.-N. Kim, J.H. Woo, Y.S. Kim, S.-K. Park, J.-H. Lee, K.-H. Lee, S.-G. Lee, D.J. Han, S.-O. Lee. Clinical and radiological features of invasive pulmonary aspergillosis in transplant recipients and neutropenic patients.
Transpl Infect Dis 2010: 12: 309–315. All rights reserved

Abstract: Invasive pulmonary aspergillosis (IPA) is an important cause of mortality in transplant recipients and in patients with

S.Y. Park[1], S.-H. Kim[1], S.-H. Choi[1], H. Sung[2], M.-N. Kim[2], J.H. Woo[1], Y.S. Kim[1], S.-K. Park[3], J.-H. Lee[4], K.-H. Lee[4], S.-G. Lee[5], D.J. Han[5], S.-O. Lee[1]

Departments of [1]Infectious Diseases, [2]Laboratory Medicine, [3]Nephrology, [4]Hematology, [5]Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

62 İnvazif Pulmoner Aspergilloz

27 (44%) SOT alıcısı

- -24 karaciğer (89%),
- -2 böbrek (7%),
- -1 kalp (4%)

35 (56%) nötropenik hasta

- -29 (83%) akut lösemi,
- -4 (11%) aplastik anemi,
- -2 (6%) miyelodisplastik sendrom

Clinical characteristics of solid organ transplantation (SOT) recipients and neutropenic patients with proven or probable invasive pulmonary aspergillosis

	SOT group ($n = 27$)	Neutropenic group ($n = 35$)	P
Thoracic CT scan findings			
Airway-invasive pattern	17/26 (65)	2/27 (7)	<0.001
Peribronchial consolidation	8/26 (31)	2/27 (7)	0.03
Centrilobular nodule	3/26 (12)	0/27 (0)	0.11
GGO	10/26 (38)	2/27 (7)	0.007
Angio-invasive pattern	9/26 (35)	25/27 (93)	<0.001
Macro-nodule	9/26 (35)	18/27 (67)	0.02
Mass-like consolidation	7/26 (27)	18/27 (67)	0.004
Halo sign	2/26 (8)	15/27 (56)	<0.001
Air crescent sign	0/26 (0)	6/27 (22)	0.01
Serum GM assay			
GM serum, n/N	26/27 (96)	35/35 (100)	0.25
GM serum positive, n/N	23/26 (89)	31/35 (89)	0.99
Median GM serum value (range)	0.82 (0.16–4.09)	1.13 (0.08–5.68)	0.26
BAL GM assay			
GM BAL, n/N	7/27 (26)	10/35 (29)	0.82
GM BAL positive, n/N	4/7 (57)	8/10 (80)	0.59
Median GM BAL value (range)	0.57 (0.17–5.91)	1.39 (0.17–3.51)	0.27
Aspergillus culture positive	3/27 (11)	3/35 (9)	0.71

Park S Y
Trans Infect Dis 2010

Fungal infections 6

Immunotherapeutic approaches to treatment of fungal diseases

Darius Armstrong-James, Gordon D Brown, Mihai G Netea, Teresa Zelante, Mark S Gresnigt, Frank L van de Veerdonk, Stuart M Levitz

Fungal infections cause morbidity worldwide and are associated with an unacceptably high mortality despite the availability of antifungal drugs. The incidence of mycoses is rising because of the HIV pandemic and because immunomodulatory drugs are increasingly used to treat autoimmune diseases and cancer. New classes of antifungal drugs have only been partly successful in improving the prognosis for patients with fungal infection. Adjunctive host-directed therapy is therefore believed to be the only option to further improve patient outcomes. Recent advances in the understanding of complex interactions between fungi and host have led to the design and exploration of novel therapeutic strategies in cytokine therapy, vaccines, and cellular immunotherapy, each of which might become viable adjuncts to existing antifungal regimens. In this report, we discuss immunotherapeutic approaches—the rationale behind their design, the challenges in their use, and the progress that is so urgently needed to overcome the devastating effect of fungal diseases.

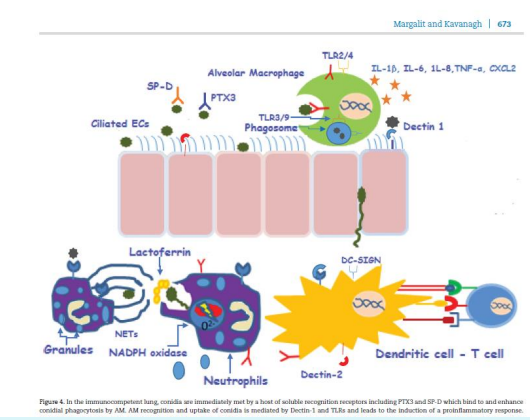
Lancet Infect Dis 2017; 17: e393–402
Published Online July 31, 2017
http://dx.doi.org/10.1016/S1473-3099(17)30442-5
This is the sixth in a Series of eight papers about fungal infections
See Series pages e383, e403, and e412
See Online/Series

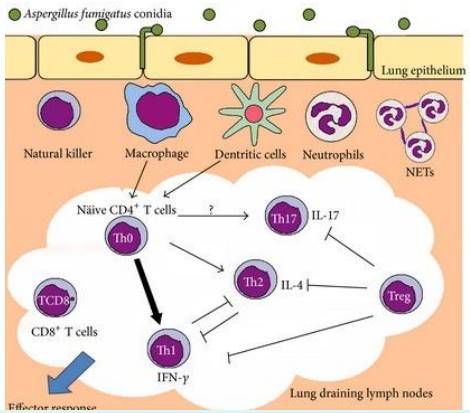
İFİ↗
Direnç↗

Diğer tedavi arayışları

Tamamlayıcı immünoterapi

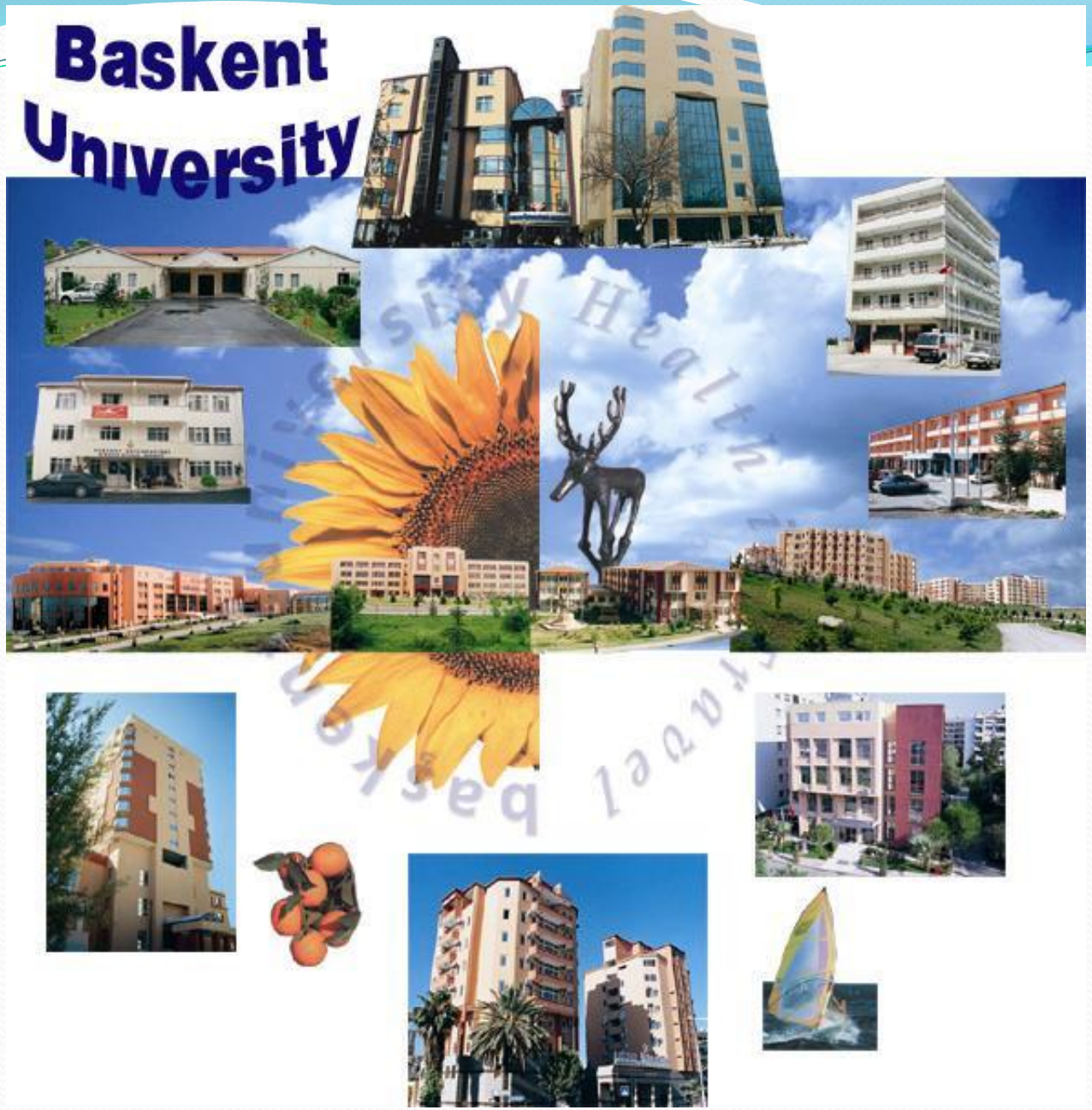
- Sitokin tedavisi
- Aşılar
- Hücresel immünoterapi





Çözünebilen immünmodulatuvar mediatörler
Ctip- Lektin reseptörlerin (dectin-1 dectin-2gb) artışı

GM-CSF
İnterferon Y


Baskent
University

- İnvazif fungal Aspergilloz
- Fungal proliferasyon ve fungal elementlerin invazyonu sonrasında doku destrüksiyonu ve infarktları söz konusu.
- ilk savunma mukosiliyer aktiviteama fumigatus çapı küçük olduğundan bunu atlatıp terminal hava yollarına ve alveollere ulaşıyor burada alveoler makrofajlar epiteyal hücreler 1,2 ve fibroblastlar
- Alvelolar makrofajlar konidiaları fagozite ediyorve öldürüyor.Nötrofil proinflamatuar yanıtını aktive ederek fagozittenten kaçmış olan hifaları öldürmesi için uyarıyor. Buradan kaçış olursa da dentritik hücreler T hücre aracılıklı fungal aktivasyonu organize ediyor.
- Epitelyal hücreler çözünebilen antimikrobiyal peptit, defensin, lizozim ve laktoferrin salgılayarak hava yolu defansını sağlıyor.
- Steroidler AMP etkisini ortadan kaldırarak konidial kolonizasyon ve invazyona neden oluyor. Nötrofillerin üzerine etki ederek hifa ların öldürülmesini engelliyor. Konidialar germtüp ve hifalar yapıyor ve salgıladıkları sekonder metobolitleri ile mukosiliyer yapının ve epitel duvar bütünlüüünü bozarak invaze oluyor.ve vasküler endotelyal hücre penetrasyonu başlıyor

- İPA da asıl patogenez anjiyoinvazyon bunun sonrasında koagülasyon kaskadı yetersiz perfüzyonnekrotik kor(kalp) burada hifalar daha da hızlı çoğalıyprçevreyi immün savunma hücreleri sarıyor periferal zon.
- İPA da iki farklı anjiyoinvazyon gelişiyor;
- En çok lokal invazyon (Abluminal penetrasyon); alveoler kapiller bariyerden başlayıp damar duvarına doğru giiden
- Daha az (luminal penetrasyon): Çok ciddi immünsüpresyon varlığında
- Kanda sirküle hifal elementlerin periferik kapiller yatakta ilerleyip uzak bir bölgede endotelyal hücreleri invaze etmesi (disseminasyon)

- İPA da tüm immünkompromizelerde klinik aynı değil, çünkü etkilemnen immünsistemler farklı
- Nötropenik hastalarda İPA histopatolojisi asp hiflerinin damar duvarını ve dokuyu invaze etmesi, tromboz,koagülatif nekroz hemoraji ve disseminasyon şeklinde
- Non-nötropenik hastada (SOT) asıl problem kortikosteroid üzerinden. Daha az hifal element ve germinasyonun farklı evrelerindeki konidyal invazyon, nötrofil ve monosit infiltrasyonu ile karekterize pnömoni alanları ve bronşiyolit, inflamatuar nekroz ve sınırlı inntraalveolar hemoraji
- IPA da CT farkı bundan
- Nötropenik hastalarda >1cm makronodül; çevresi halosign
- SOT da makronodüller, buzlu cam, periferal konsolidasyon vb.