# Yetişkinlerde Uzun Süreli Glukokortikoid Tedavileriyle İlişkili Fırsatçı İnfeksiyon Riski ve Önlenmesi:

# Fungal İnfeksiyonlar

**Ayşe Özlem METE**

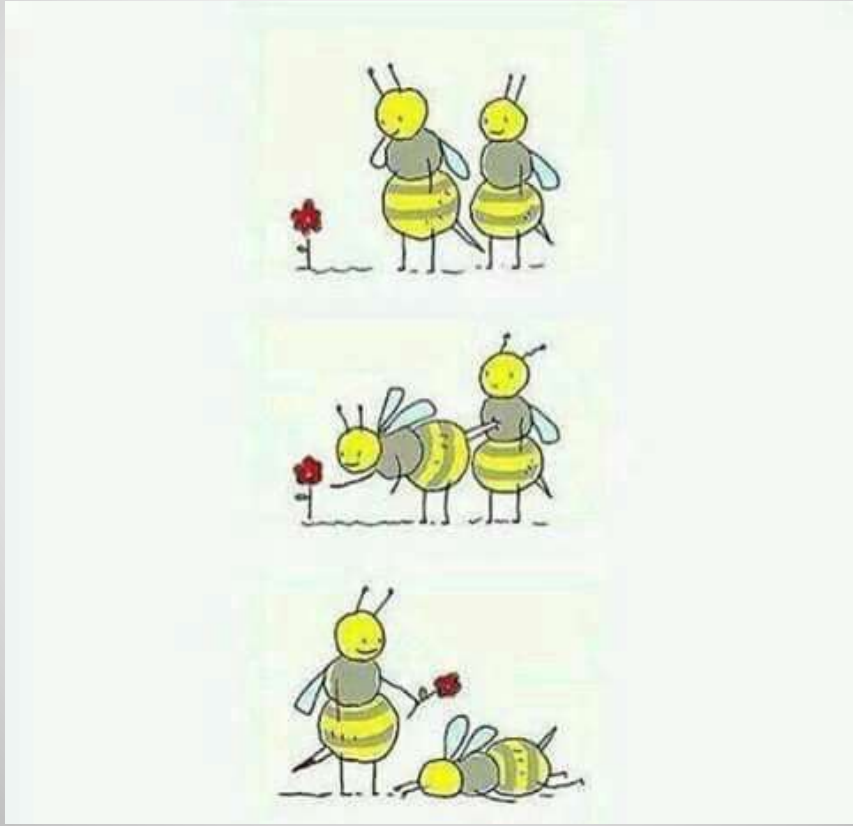
Gaziantep Üniversitesi Tıp Fakültesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji ABD


THE
DOUBLE
BLADED
SWORD


PROS
CONS

# Kaş yaparken…




SHORT TERM
LONG TERM


LOW RISK
HIGH RISK

# Profilaksi gerekli mi? Neden???

Karıştırıcı faktörler

Karıştırıcı faktörler

Karıştırıcı faktörler

Karıştırıcı faktörler

# Fungal İnfeksiyonlar

- 4-4.5 milyon/yıl fungal infeksiyon
- 1milyon yüzeyel mikoz
- 1-1.7 milyon/yıl ölüm
  - İmmünsüprese hastalar

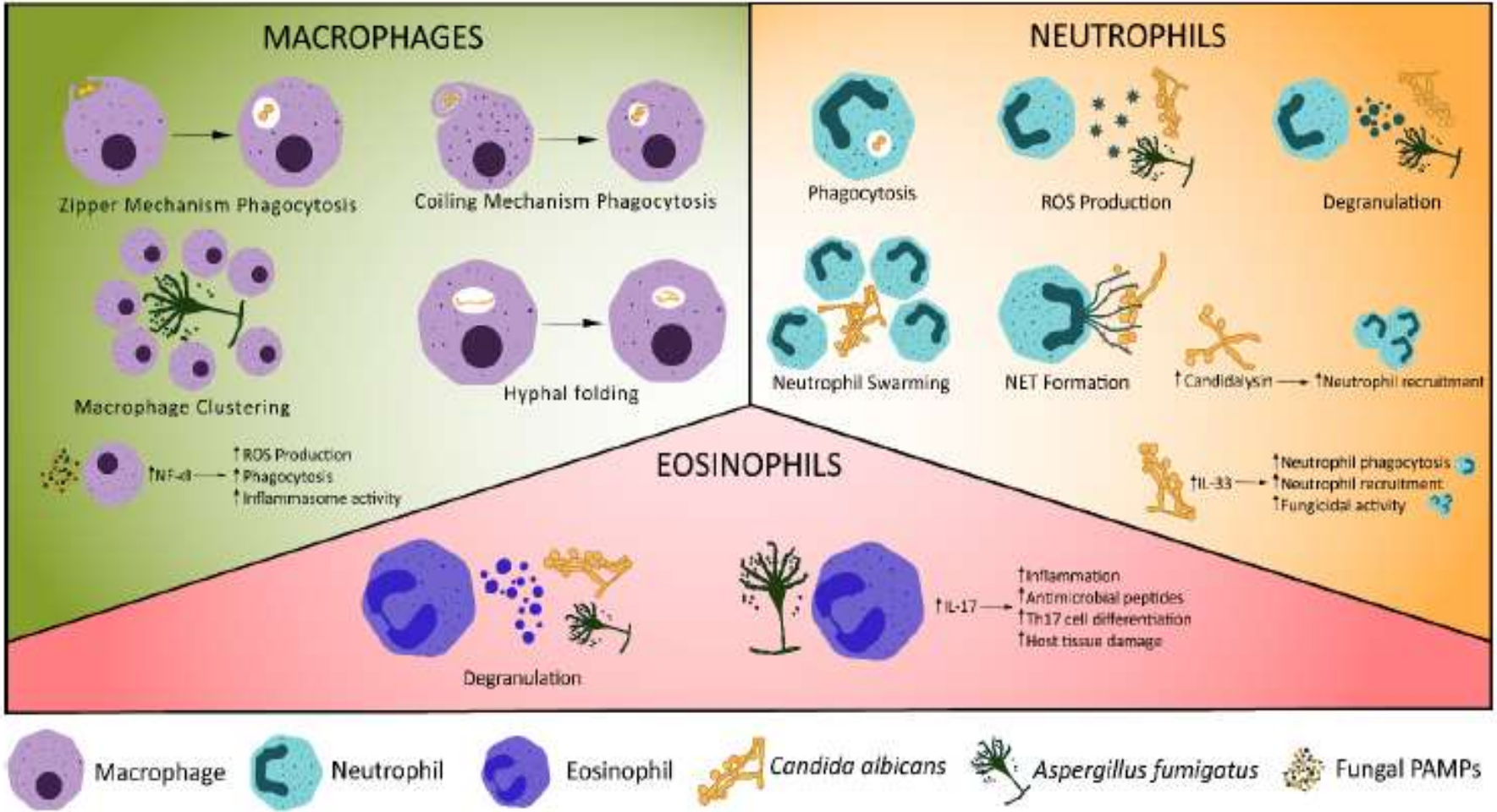
Kainz, K. Microb. Cell **2020**, 7,143–145
Bongomin F. J. Fungi 2017, 3, 57
Last A. FEMS MicrobiolRev. 2021;45(5)

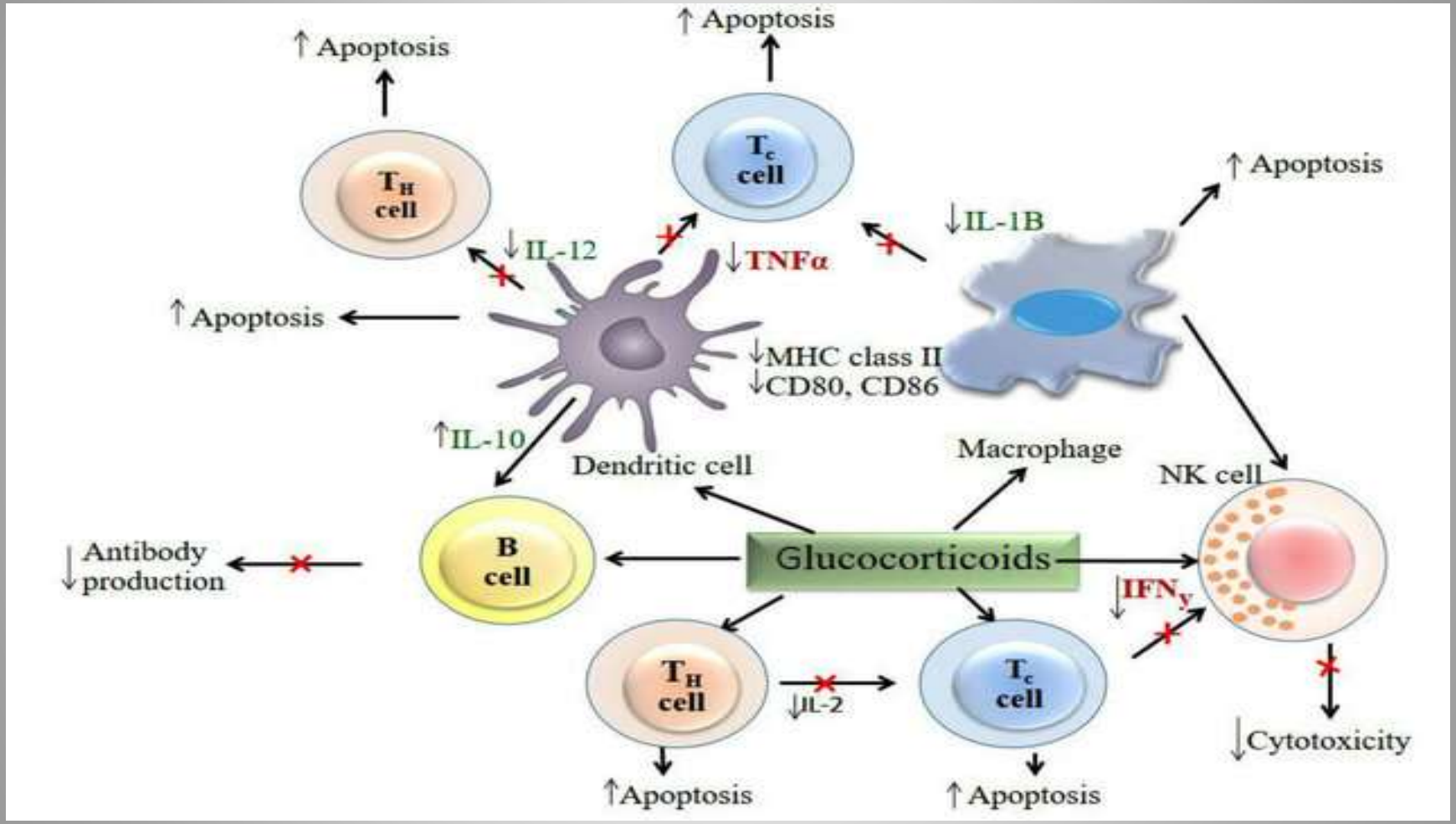
# Long-term prednisone treatment causes fungal microbiota dysbiosis and alters the ecological interaction between gut mycobiome and bacteriome in rats

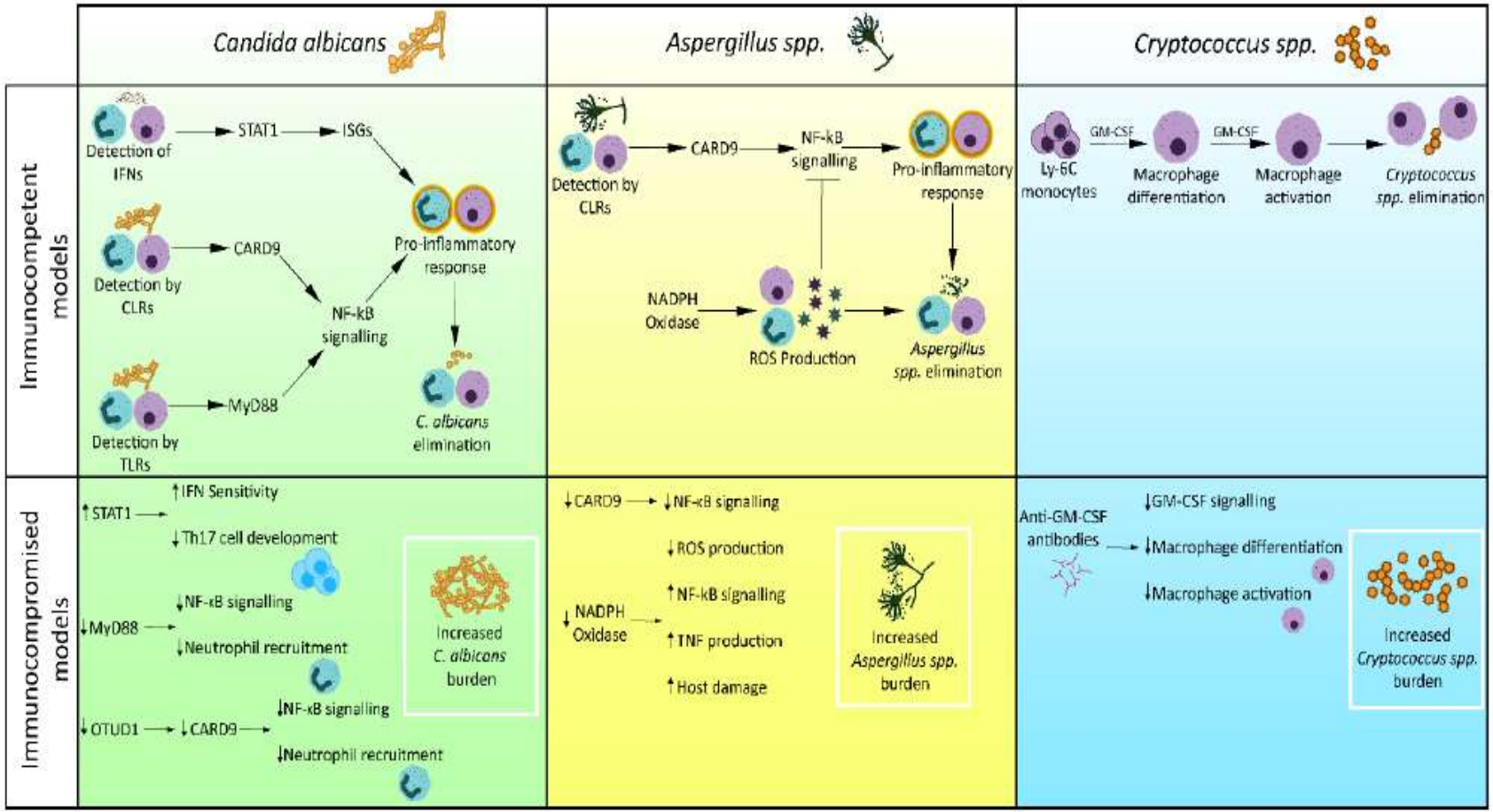
Wenyan Li[1†], Yun Shu[1†], Jing Zhang[1], Mengmeng Wu[1], Guang-hua Zhu[1], Wen-yan Huang[1], Li Shen[2*] and Yulin Kang[1*]

[1]Department of Nephrology and Rheumatology, Shanghai Children's Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China, [2]Department of Cardiothoracic Surgery, Shanghai Children's Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

6 haftalık prednizon tedavisi
Fekal örnekleme
Aspergillus artışı


MACROPHAGES
Zipper Mechanism Phagocytosis
Coiling Mechanism Phagocytosis
Macrophage Clustering
Hyphal folding
↑NF-κB
↑ROS Production
↑Phagocytosis
↑Inflammasome activity
NEUTROPHILS
Phagocytosis
ROS Production
Degranulation
Neutrophil Swarming
NET Formation
↑Candidalysin
↑Neutrophil recruitment
EOSINOPHILS
↑IL-33
↑Neutrophil phagocytosis
↑Neutrophil recruitment
↑Fungicidal activity
Degranulation
↑IL-17
↑Inflammation
↑Antimicrobial peptides
↑Th17 cell differentiation
↑Host tissue damage
Macrophage
Neutrophil
Eosinophil
Candida albicans
Aspergillus fumigatus
Fungal PAMPs


↑ Apoptosis
↑ Apoptosis
↑ Apoptosis
$T_H$ cell
$T_c$ cell
↓IL-12
↓TNFα
↓IL-1B
↑ Apoptosis
↑ Apoptosis
↓MHC class II
↓CD80, CD86
↑IL-10
Dendritic cell
Macrophage
NK cell
↓ Antibody production
B cell
Glucocorticoids
↓$IFN_\gamma$
$T_H$ cell
↓IL-2
$T_c$ cell
↓Cytotoxicity
↑Apoptosis
↑ Apoptosis


Candida albicans
Aspergillus spp.
Cryptococcus spp.
Immunocompetent models
Detection of IFNs
STAT1
ISGs
Detection by CLRs
CARD9
Pro-inflammatory response
NF-kB signalling
Detection by TLRs
MyD88
C. albicans elimination
Detection by CLRs
CARD9
NF-kB signalling
Pro-inflammatory response
NADPH Oxidase
ROS Production
Aspergillus spp. elimination
Ly-6C monocytes
GM-CSF
Macrophage differentiation
GM-CSF
Macrophage activation
Cryptococcus spp. elimination
Immunocompromised models
↑STAT1
↑IFN Sensitivity
↓Th17 cell development
↓NF-κB signalling
↓MyD88
↓Neutrophil recruitment
↓NF-κB signalling
↓OTUD1
↓CARD9
↓Neutrophil recruitment
Increased C. albicans burden
↓CARD9
↓NF-κB signalling
↓ROS production
↓NADPH Oxidase
↑NF-kB signalling
↑TNF production
↑Host damage
Increased Aspergillus spp. burden
Anti-GM-CSF antibodies
↓GM-CSF signalling
↓Macrophage differentiation
↓Macrophage activation
Increased Cryptococcus spp. burden

# İmmün Sisteme Etkileri:

- Transkripsiyonel değişiklikler
- Post-translasyonel değişiklikler

- Kan hücre sayıları
- Hücre fonksiyonları
- Lökosit adezyonu
- Fagositoz
- B hücre immünoglobulin

**Uzun süre: Adaptif immün yanıt…

| Pattern Recognition Receptor | Localisation | Cell Expression | Adaptor Proteins | Effectors | Pathogen-/Damage-Associated Molecular Patterns Recognised | Fungal Species |
|---|---|---|---|---|---|---|
| Dectin-1 | Plasma membrane | Monocytes, macrophages, dendritic cells, neutrophils, mast cells, some T cells | hemITAM | IL-2, IL-6, IL-10, IL-23 | β-1,3-glucans | *Candida spp., C. neoformans, A. fumigatus, H. capsulatum, S. cerevisiae, P. brasiliensis* |
| Dectin-2 | Plasma membrane | Monocytes, macrophages, dendritic cells, neutrophils | ITAM-FcRγ | TNFα | Mannose | *C. albicans, C. glabrata, C. neoformans, A. fumigatus, H. capsulatum* |
| Mincle | Plasma membrane | Monocytes, macrophages, dendritic cells, neutrophils, mast cells, some B cells | ITAM-FcRγ | NF-κB, IL-1, IL-6, IL-10 IL-12, IL-23 | α-mannose, glycoeroglycolipid, mannosyl fatty acids, MSG/gpA | *A. fumigatus, C. albicans, P. carinii, Malassezia spp.* |
| DC-SIGN | Plasma membrane | Macrophages, dendritic cells, activated B cells | LSP1 | IL-10 | Mannose, N-linked mannans, galactomannans | *C. albicans, C. neoformans, A. fumigatus, S. cerevisiae* |
| Mannose Receptor | Plasma membrane | Macrophages, Kupffer cells, endothelial cells | Associated with FcRγ and GBR2, exact mechanism unknown | TNF, IL-1β | Mannose, α-glucans, chitin | *C. albicans, C. neoformans, A. fumigatus, H. capsulatum, S. cerevisiae, P. brasiliensis* |
| MDA5 | Cytoplasm | Monocytes, macrophages, dendritic cells, B cells, epithelial cells, endothelial cells, fibroblasts | CARDs, MAVs | NF-κB, Type I IFN, Type III IFN, TNFα, IL-12, | dsRNA | *C. albicans, A. fumigatus* |

PRRs (Konak)

PAMPs

| Corticosteroid Drug | Treatment for | Molecular formula |
|---|---|---|
| Betamethasone | Dermatitis | $C_{22}H_{29}FO_5$ |
| Budesonide | Asthma, noninfectious rhinitis, nasal polyposis | $C_{25}H_{34}O_6$ |
| Cortisone | IgE-mediated allergies | $C_{21}H_{28}O_5$ |
| Dexamethasone | Inflammation, rheumatoid arthritis | $C_{22}H_{29}FO_5$ |
| Hydrocortisone | Dermatitis | $C_{21}H_{30}O_5$ |
| Methylprednisolone | Arthritis, Bronchial inflammation | $C_{22}H_{30}O_5$ |
| Prednisolone | Asthma, rheumatoid arthritis, ulcerative colitis, Crohn's disease | $C_{21}H_{28}O_5$ |
| Prednisone | Systemic lupus erythematosus, Bell's palsy, asthma, dermatitis | $C_{21}H_{26}O_5$ |
| Triamcinolone | Eczema, diabetic retinopathy | $C_{21}H_{27}FO_6$ |

# Corticosteroid Conversion Chart

| Glucocorticoid | Approximate Equivalent Dose (mg) | Relative Anti-Inflammatory (Glucocorticoid) Potency | Relative Mineralocorticoid (Salt Retaining) Potency | Biological Half-Life (Hours) |
|---|---|---|---|---|
| **Short-Acting** | | | | |
| Cortisone | 25 | 0.8 | 0.8 | 8 - 12 |
| Hydrocortisone | 20 | 1.0 | 1.0 | 8 - 12 |
| **Intermediate-Acting** | | | | |
| Methylprednisolone | 4 | 5 | 0.5 | 18 - 36 |
| Prednisolone | 5 | 4 | 0.8 | 18 - 36 |
| Prednisone | 5 | 4 | 0.8 | 18 - 36 |
| **Long-Acting** | | | | |
| Dexamethasone | 0.75 | 25 | 0.0 | 36 - 54 |

Meikle AW et al. Potency and Duration of Action of Glucocorticoids. AM J of Med. 1977. 63 (2):200 - 207. PMID: 888843

- Doz
- Süre
- Altta yatan hastalık
- Eş zamanlı ilaçlar
  - İmmünsüpresanlar
  - İmmünmodülatörler

## Yüksek Doz

- Çocukta--- >1mg/kg/gün Prednizon
- Erişkinde--- >40mg/gün

## Uzun Süre

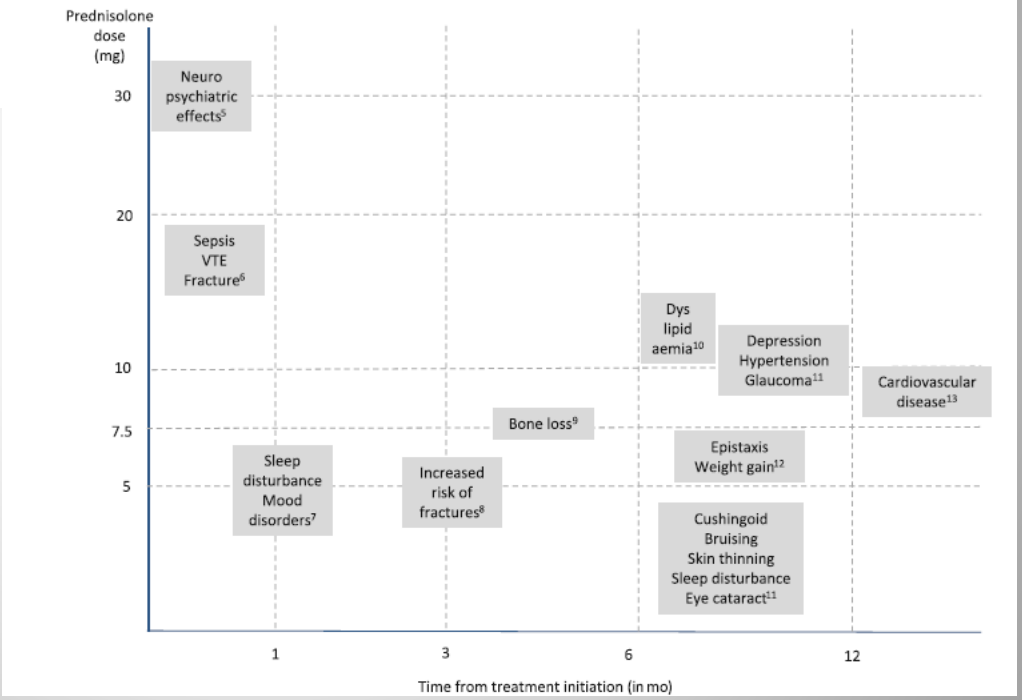
- >2 hafta?
- >4 hafta?
- Risk ne zaman artar?

Received: 14 July 2020 | Revised: 9 November 2020 | Accepted: 12 November 2020
DOI: 10.1111/bcp.14679

INVITED REVIEW ARTICLE

# Is there a safe and effective way to wean patients off long-term glucocorticoids?

Emma Baker[1,2]



*Clinical Infectious Diseases*

STATE OF THE ART REVIEW

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

# Unintended Consequences: Risk of Opportunistic Infections Associated With Long-term Glucocorticoid Therapies in Adults

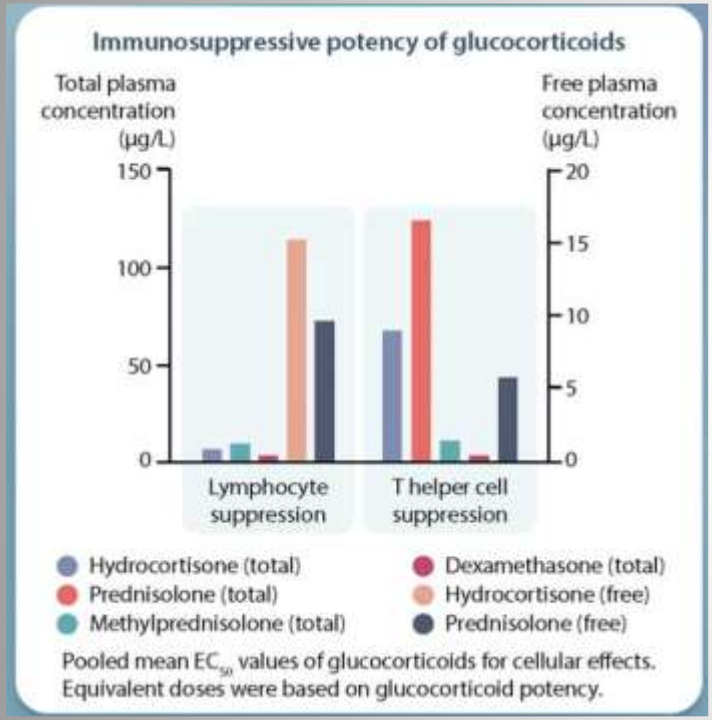
**Daniel B. Chastain,[1] Megan Spradlin,[2] Hiba Ahmad,[2] and Andrés F. Henao-Martínez[3]**

[1]Department of Clinical and Administrative Pharmacy, University of Georgia College of Pharmacy, Albany, Georgia, USA; [2]Division of Medical Oncology, University of Colorado School of Medicine, Aurora, Colorado, USA; and [3]Division of Infectious Diseases, University of Colorado, Aurora, Colorado, USA

**Table 1. Immunologic Effects of Glucocorticoids and Resultant Clinical Implications**

| Cell Type | Glucocorticoid Effects On Cellular Responses | Laboratory Finding(s) | Clinical Implications[a] |
|---|---|---|---|
| Neutrophils [11–15] | ↑ Production<br>↓ Extravasation | Neutrophilia and impaired phagocytic activity | ↑ Risk of common bacterial and viral infections [52, 53] |
| Eosinophils [16, 17] | ↑ Apoptosis<br>↓ TLR signaling | Eosinopenia | ↑ Risk of fungal infections |
| Basophils [18] | ↑ Apoptosis | Basopenia and decreased histamine release | Limited clinical relevance |
| Mast cells [19–21] | ↓ Cytokines, chemokine, and arachidonic acid derivative production, as well as FcεRI expression | Decreased histamine release and antiallergic actions | Limited clinical relevance |
| Macrophages and monocytes [11, 12, 22–26, 31, 32] | ↑ Pro-resolution cytokine<br>↓ Inflammatory cytokine production, TLR signaling | Limited impact on macrophage function, although impaired opsonization and $T_H$-cell activation | ↑ Risk of intracellular infections (eg, *Legionella* species, *Salmonella* species), MTB, and fungal infections |
| Natural killer cells [33, 34] | ↑ Activation<br>↓ Inflammatory cytokine production | Reduced cytotoxicity | ↑ Risk of viral infections or reactivation (eg, HSV, HZ, CMV) and fungal infections |
| Dendritic cells [39] | ↑ Apoptosis<br>↓ Inflammatory cytokine production, antigen presentation, maturation | Decreased T-cell activity | Limited clinical relevance (although contributes significantly to T-cell response) |
| $T_H$ cells (CD4 cells) [35, 36, 38, 42, 45] | ↑ Apoptosis<br>↓ $T_H1 > T_H2$ and $T_H17$ cell response and inflammatory cytokine production, T-cell signaling | Decreased number of circulating $T_H$ cells with shift from cell-mediated immunity to humoral-mediated immunity | ↑ Risk of bacterial, viral, and fungal infections or reactivation, including intracellular (eg, *Legionella* species, *Salmonella* species) and opportunistic infections, (eg, MTB, *P. jirovecii*, candidiasis, cryptococcosis, aspergillosis, SHS) |
| Cytotoxic T cells (CD8+ T cells) [37] | ↑ Apoptosis<br>↓ Inflammatory cytokine production, T-cell signaling | Reduced cytotoxicity | ↑ Risk of viral infections or reactivation (eg, HSV, HZ, CMV) |
| B cells [4, 46–48] | ↑ BAFF, IL-10, Blimp-10, apoptosis<br>↓ B-cell receptor signaling and TLR-7 signaling | Decreased number of circulating B cells and lower plasma immunoglobulins, except for IgE | ↑ Risk of *Neisseria meningitides, Haemophilus influenzae, Streptococcus pneumoniae* [50, 51] |

↑, indicates stimulatory effects; ↓, indicates inhibitory effects.




- GK'ler alındıktan 4-6 saat sonra immunite
- Yüksek dozda daha hızlı
- Hem T Hem de B hücreler etkilenir ancak özellikle CD4 hücrelere etkisi daha derin…
- GK-infeksiyon iyi tanımlanmış bir ilişki ancak kimin nasıl etkileneceği multifaktöriyel…

**Table 5. Recommendations to Prevent Acute Infections or Reactivation of Opportunistic Infections in Patients Requiring Glucocorticoids**

| Opportunistic Infection | Recommended Indications | Recommendations for Prevention |
|---|---|---|
| Patients with AIIRD requiring glucocorticoids | | |
| Latent TB | • Patients treated with ≥15 mg PEQ/d for ≥28 d, but preferably before initiating glucocorticoid therapy<br>• Screening for latent TB may be indicated in those treated with <15 mg PEQ/d with a history of alcohol abuse, smoking, and living with people with TB or in endemic countries<br>• Screening for latent TB may be indicated before initiating pulse dose glucocorticoid therapy in those already receiving glucocorticoid therapy at baseline | • IGRA preferred over TST<br>• Further recommendations are available from the US Preventive Services Task Force [125] and EULAR [54] |
| PJP | • Patients treated with ≥15 mg PEQ/d for ≥14 to 28 d<br>• Prophylaxis may be indicated in patients with a history of PJP, those treated with lower doses of glucocorticoids if 1 or more additional risk factors for PJP are present (eg, solid-organ transplantation, acute lymphocytic leukemia, lymphopenia [< 600 lymphocytes/mm$^3$ or <300–350 CD4 cells/mm$^3$ before or during treatment with glucocorticoids], concomitant immunosuppressive medications, underlying pulmonary disease, older age), or individuals treated with glucocorticoid injection or pulse therapy | • TMP/SMX 40 mg/200 mg once daily or 80 mg/400 mg once daily or 3 times weekly<br>• TMP/SMX 80 mg/400 mg 3 times weekly in patients with renal dysfunction (CrCl: 15–30 mL/min)<br>• Higher doses (160 mg/800 mg) are not expected to provide added benefit but may increase the risk of adverse effects<br>• Further recommendations are available from EULAR [54] |
| Cryptococcosis | Symptomatic patients treated with glucocorticoid therapy who are at risk of cryptococcosis | • Serum CrAg test |
| HZ | • Patients treated with glucocorticoid therapy, but preferably before initiating glucocorticoid therapy<br>• Vaccination may be indicated in those with additional risk factors for HZ (eg, age, chronic comorbidities, or concomitant immunosuppressive medications) | • Vaccination with RZV (Sh<br>• Antiviral prophylaxis is no<br>• Further recommendation |
| SHS | Patients treated with glucocorticoid therapy who were born or residing for more than 6 mo in endemic countries (eg, Asia, Oceania, Africa, South America, the Caribbean, and Mediterranean countries), but preferably before initiating glucocorticoid therapy | • Stool sample should be s to serum IgG against *Str*<br>• Nonpharmacological prev prevent *Strongyloides* inf or sewage, wear protecti<br>• Further recommendations are available from CATMAT [148] |

SOT
Lösemi-lenfoma
İleri yaş
CD4<300-350
Eş zamanlı immunsupresan

**Table 5. Recommendations to Prevent Acute Infections or Reactivation of Opportunistic Infections in Patients Requiring Glucocorticoids**

| Opportunistic Infection | Recommended Indications | Recommendations for Prevention |
|---|---|---|
| Patients treated with glucocorticoid therapy for irAEs associated with CPIs | | |
| Latent TB | Before initiating glucocorticoid therapy, but preferably before starting CPIs | • IGRA<br>• Further recommendations are available from the NCCN [94] |
| PJP | Patients treated with ≥20 mg PEQ/d for ≥28 d | • TMP/SMX 80 mg/400 mg once daily or 160 mg/800 mg 3 times weekly, or if TMP/SMX intolerant, then<br>• Atovaquone 1500 mg once daily, or<br>• Dapsone 100 mg once daily, or<br>• Pentamidine (aerosolized inhalation or intravenous) |
| Cryptococcosis | Symptomatic patients treated with glucocorticoid therapy who are at risk of cryptococcosis | • Serum CrAg test |
| HZ | Before initiating glucocorticoid therapy, but preferably before starting CPIs | • Vaccination with RZV (Shingrix) before initiating glucocorticoid therapy<br>• Antiviral prophylaxis is determined by standard prevention protocols in specific hematologic malignancy populations or those receiving concomitant alemtuzumab<br>• Further recommendations are available from the NCCN [94] |
| SHS | Before initiating glucocorticoid therapy, but preferably before starting CPIs | • Stool sample should be screened for ova and parasites in addition to serum IgG against *Strongyloides stercoralis*<br>• Nonpharmacological preventive measures should be discussed to prevent *Strongyloides* infection (eg, avoid contact with fecal matter or sewage, wear protective clothing around soil) |

Recommend

# 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections adults with autoimmune inflammatory rheumatic diseases

George E Fragoulis [1,2] Elena Nikiphorou [3,4] Mrinalini Dey [5,6] Sizheng Steven Zhao,[7] Delphine Sophie Courvoisier [8] Laurent Arnaud [9] Fabiola Atzeni,[10] Georg MN Behrens,[11] Johannes WJ Bijlsma,[12] Peter Böhm,[13] Costas A Constantinou,[14] Silvia Garcia-Diaz,[15] Meliha Crnkic Kapetanovic,[16] Kim Lauper [7,17] Mariana Luís [18] Jacques Morel,[19] György Nagy [20,21] Eva Poleverino,[22] Jef van Rompay,[23] Marco Sebastiani [24] Anja Strangfeld [ ] Annette de Thurah [26,27] James Galloway [3,4] Kimme L Hyrich [7,28]

**Pneumocystis jirovecii pneumonia (PCP)**

⇒ Does the risk of *Pneumocystis jirovecii* pneumonia (PCP) differ according to underlying AIIRD (eg, giant cell arteritis, systematic literature review, ANCA-associated vasculitis, etc)?

⇒ What is the added risk of PCP in patients treated with combination glucocorticoids/immunosuppressive therapies compared to those receiving glucocorticoids along?

⇒ What is the safest and most effective regimen for PCP prophylaxis?

⇒ How long should patients at risk for PCP receive prophylaxis?

Prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) should be considered in patients with AIIRD in whom high doses of glucocorticoids are used, especially in combination with immunosuppressants* and depending on the risk–benefit ratio.

Prophylaxis for PCP has been mostly examined in AIIRD patients treated with glucocorticoids. Although the minimum dose and duration of glucocorticoid treatment above which prophylaxis is recommended is not defined, evidence suggests that in daily doses >15–30 mg of prednisolone or equivalent for >2–4 weeks, prophylaxis is beneficial.[182–186] Most studies do not focus on a specific AIIRD. Therefore, it was not possible to make recommendations for PCP prophylaxis in individual diseases although the risk for PCP infection might be significantly different.[187] Data specifically addressing the contribution of other antirheumatic drugs in PCP development are limited.[188 189] On the other hand, it has been shown that coadministration of immunosuppressants with glucocorticoids[184 185 190] increase the risk for PCP. Other features including persistent lymphopenia,[5 6 184 185] older age and pre-existing lung disease are also considered risk factors for PCP.[4–6]

The most commonly used prophylaxis scheme is trimethoprim/sulfamethoxazole (TMP-SMX) 480 mg/day (single-strength) or 960 mg three times a week; of note, there is some evidence that reduced doses (eg, half-strength, daily) may also be effective and associated with fewer adverse events .[191–195] It should be noted that adverse events related to TMP-SMX (eg, nausea, headache, rash) are common, affecting about 20% of patients.[196] Concerns for higher adverse event rates have been expressed for individuals treated with methotrexate (in specific relation to the combination of TMP and MTX and the risk of cytopenia) or in patients with systemic lupus erythematosus (SLE).[187 197]

Alternative prophylactic medications include atovaquone, dapsone or nebulised pentamidine. Although there is some disagreement in the literature,[198] it seems that they are equally effective compared with TMP-SMX[199–201]; however, their usage is limited by factors like cost or need for hospital administration.[2]

# Korunma:

- İnvaziv Aspergilloz:
  - Hematolojik malignite
  - NCCN
  - SOT
- Cryptococcosis:
  - CrAg
- PJP:
  - Doz/süre
  - TMP/SMX profilaksisi*

Biol Blood Marrow Transplant 22 (2016) 1102–1107

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

# Association of Cumulative Steroid Dose with Risk of Infection after Treatment for Severe Acute Graft-versus-Host Disease

Yayoi Matsumura-Kimoto [1,2], Yoshihiro Inamoto [1,*], Kinuko Tajima [1], Akihisa
Takashi Tanaka [1], Tsuneaki Hirakawa [1], Kazuko Ino [1], Yu Asao [1], Hiroyuki Tar
Chika Kono [1], Wataru Takeda [1], Keiji Okinaka [1], Shigeo Fuji [1], Saiko Kurosaw
Ryuji Tanosaki [3], Takuya Yamashita [1], Takahiro Fukuda [1]

[1] Department of Hematopoietic Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo, Japan
[2] Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan
[3] Department of Blood Transfusion and Cellular Therapy, National Cancer Center Hospital, Tokyo, Japan

2002-2014, HSCT 805, 91 GVHD
9-68 yaş (51)
- 39 (%43) AML veMDS
- 17 (%19) ALL
- 17 (%19) Lenfoma
- 18 (%20) diğer

%35 myeloablasyon
%65 düşük yoğunluklu rejimler
Siklosporin/Takrolimus + MTX/ MMF

| | |
|---|---|
| Donor-patient CMV serostatus | |
| Either positive | 87 (96) |
| Both negative | 3 (3) |
| Unknown | 1 (1) |
| GVHD prophylaxis | |
| Tacrolimus-based | 33 (36) |
| Cyclosporine-based | 58 (64) |
| GVHD grade at onset | |
| II | 16 (18) |
| III-IV | 75 (82) |
| Maximum GVHD grade | |
| III | 74 (81) |
| IV | 17 (19) |
| Site of GVHD at onset | |
| Skin | 60 (66) |
| Liver | 26 (29) |
| Gut | 78 (86) |

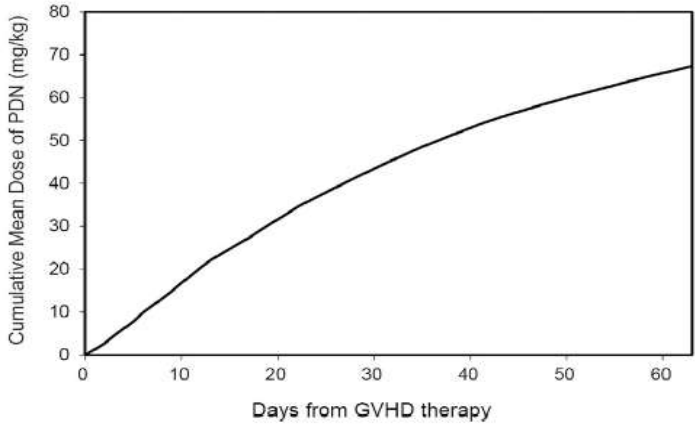



**Figure 1.** Cumulative dose of prednisolone-equivalent glucocorticoids after initial treatment of acute GVHD.

İlk 4 haftada ortalama 41 mg/kg kümülatif doz

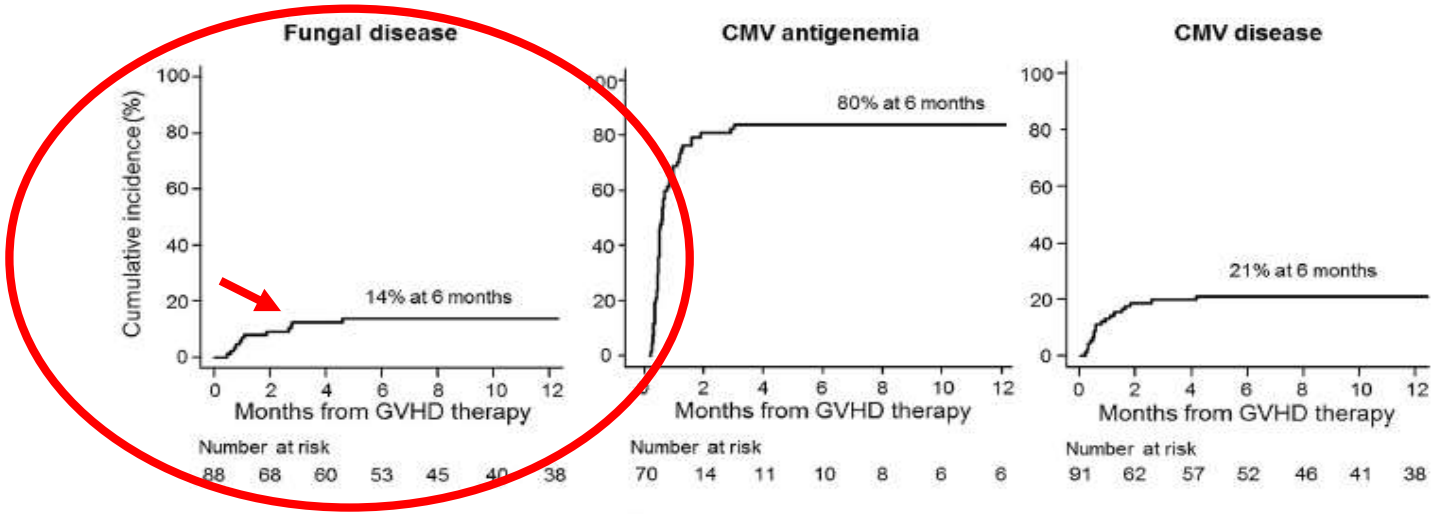
6. Ayda fungal infeksiyon: %14 (13)

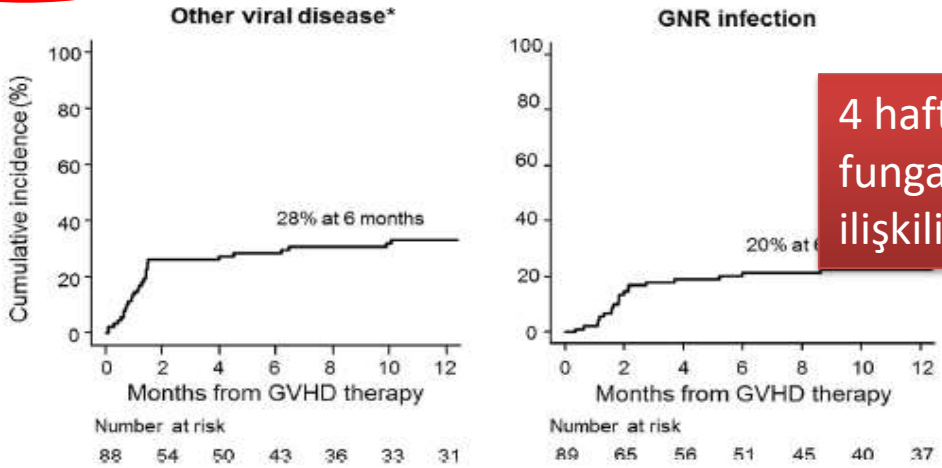
-11 İPA

-2 Kandidemi

-2 (1-3 β glukan/Görüntüleme)

Ortalama 32. gün




4 haftada 55mg/kg fungal infeksiyonlarla ilişkili

**Table 2**
Univariate Analysis of Risk Factors Associated with Individual Infections

| Factor | Fungal Disease | | CMV Antigenemia | | CMV Disease | | Other Viral Disease* | | GNR Infection | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P |
| Patient age | | | | | | | | | | |
| ≤50 Yr | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| >50 Yr | .28 (.08-1.03) | .55 | 1.66 (.98-2.82) | .06 | 1.73 (.68-4.40) | .25 | .95 (.46-1.97) | .89 | 1.40 (.62-3.18) | .43 |
| Patient gender | | | | | | | | | | |
| Male | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| Female | 2.43 (.82-7.26) | .11 | .90 (.52-1.56) | .71 | 1.40 (.56-3.48) | .47 | .53 (.23-1.25) | .15 | 1.43 (.62-3.31) | .41 |
| Female donor to male patient | .30 (.04-2.29) | .24 | .72 (.36-1.44) | .36 | .74 (.22-2.54) | .63 | 1.11 (.45-2.76) | .82 | 1.12 (.41-3.03) | .83 |
| Disease | | | | | | | | | | |
| AML/MDS | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| ALL | 1.63 (.36-7.30) | .52 | .88 (.44-1.78) | .73 | .53 (.15-1.91) | .33 | 1.95 (.71-5.37) | .20 | .91 (.31-2.67) | |
| Lymphoma | 2.84 (.71-11.3) | .14 | .90 (.40-2.06) | .80 | .56 (.16-2.02) | .38 | 2.19 (.79-6.05) | .13 | .45 (.10-2.06) | |
| Others | 1.07 (.19-5.83) | .94 | .93 (.46-1.87) | .84 | .32 (.07-1.45) | .14 | 2.30 (.83-6.34) | .11 | 1.11 (.40-3.05) | |
| Disease risk | | | | | | | | | | |
| Standard | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| High | 1.50 (.46-4.88) | .50 | .96 (.56-1.66) | .90 | .44 (.18-1.10) | .08 | 1.19 (.56-2.51) | .66 | 1.53 (.64-3.84) | |
| Graft source | | | | | | | | | | |
| Bone marrow | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| Peripheral blood stem cell | .76 (.26-2.27) | .63 | 1.16 (.67-2.02) | .59 | .59 (.23-1.52) | .27 | 1.34 (.62-2.94) | .46 | .50 (.22-1.16) | |
| Cord blood | NA† | NA† | 1.50 (.44-5.08) | .51 | 1.80 (.39-8.30) | .46 | 1.92 (.42-8.79) | .40 | 1.50 (.19-11.8) | |
| Donor | | | | | | | | | | |
| Related | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| Unrelated | .96 (.31-2.92) | .94 | 1.09 (.63-1.86) | .76 | 2.14 (.86-5.33) | .10 | .80 (.38-1.69) | .55 | 1.61 (.71-3.66) | |
| HLA matching | | | | | | | | | | |
| Match | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| Mismatch | .92 (.30-2.83) | .89 | 1.74 (1.03-2.96) | .04 | 1.14 (.46-2.85) | .77 | 1.27 (.61-2.63) | .53 | .84 (.35-1.97) | |
| Conditioning intensity | | | | | | | | | | |
| Myeloablative | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| Reduced intensity | .49 (.17-1.47) | .21 | 1.34 (.77-2.33) | .30 | 1.66 (.60-4.60) | .33 | 1.28 (.58-2.82) | .53 | 1.49 (.61-3.62) | |
| Total body irradiation | | | | | | | | | | |
| None | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| 2-4 Gy | NA† | NA† | .93 (.46-1.89) | .85 | 2.01 (.78-5.21) | .15 | .82 (.33-2.04) | .67 | 1.85 (.74-4.68) | |
| 12 Gy | .74 (.20-2.68) | .64 | .87 (.44-1.72) | .69 | .21 (.03-1.66) | .14 | .36 (.12-1.21) | .10 | .57 (.16-2.00) | |
| GVHD prophylaxis | | | | | | | | | | |
| Tacrolimus-based | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| Cyclosporine-based | .50 (.17-1.48) | .21 | 1.11 (.64-1.93) | .71 | 1.87 (.67-5.19) | .23 | 2.3 (.98-5.42) | .06 | 1.16 (.49-2.73) | |
| Time from transplantation to GVHD onset | | | | | | | | | | |
| >26 d | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| ≤ 26 d | .92 (.31-2.74) | .88 | .75 (.44-1.27) | .28 | 3.63 (1.21-10.9) | .02 | 3.98 (1.62-9.80) | .003 | 1.40 (.59-3.35) | |
| GVHD grade at onset | | | | | | | | | | |
| II | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| III-IV | .47 (.06-3.63) | .47 | 1.50 (.73-3.07) | .27 | .52 (.12-2.26) | .38 | 1.85 (.79-4.35) | .16 | 1.10 (.37-3.27) | |
| lymphocyte count at onset of glucocorticoid treatment | | | | | | | | | | |
| ≥ Median (550/μL) | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| < Median | .89 (.27-2.91) | .84 | .96 (.55-1.67) | .89 | 3.17 (1.13-8.90) | .03 | 1.82 (.83-3.96) | .13 | 2.69 (1.08-6.69) | |
| Initial glucocorticoid dose | | | | | | | | | | |
| 1 mg/kg | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| < 1 mg/kg | .26 (.03-2.05) | .20 | 1.40 (.75-2.61) | .29 | 1.13 (.40-3.22) | .82 | .53 (.18-1.57) | .25 | .33 (.08-1.41) | |
| > 1 mg/kg | .35 (.04-2.70) | .31 | 1.50 (.71-3.14) | .29 | .54 (.12-2.41) | .42 | 1.60 (.67-3.83) | .29 | .87 (.29-2.60) | |
| Second-line treatment‡ | 4.37 (1.34-14.3) | .02 | .59 (.18-1.95) | .38 | .55 (.07-4.20) | .57 | 1.70 (.59-4.96) | .33 | 2.13 (.72-6.31) | |

* Other viral disease included ADV, BKV, herpes simplex virus (HSV), HHV-6, Epstein-Barr virus (EBV), and VZV.
† NA (not applicable) due to insufficient numbers of events for analysis.
‡ A time-varying covariate.

İki yönlü ilişki:
GVHD > grade 2
Prednizon >1-2 mg/kg

| | | |
|---|---|---|
| GVHD prophylaxis | | |
| Tacrolimus-based | 1.00 (reference) | |
| Cyclosporine-based | .50 (.17-1.48) | .21 |
| Time from transplantation to GVHD onset | | |
| >26 d | 1.00 (reference) | |
| ≤ 26 d | .92 (.31-2.74) | .88 |
| GVHD grade at onset | | |
| II | 1.00 (reference) | |
| III-IV | .47 (.06-3.63) | .47 |
| Lymphocyte count at onset of glucocorticoid treatment | | |
| ≥ Median (550/μL) | 1.00 (reference) | |
| < Median | .89 (.27-2.91) | .84 |
| Initial glucocorticoid dose | | |
| 1 mg/kg | 1.00 (reference) | |
| < 1 mg/kg | .26 (.03-2.05) | .20 |
| > 1 mg/kg | .35 (.04-2.70) | .31 |
| Second-line treatment‡ | 4.37 (1.34-14.3) | .02 |

National Comprehensive Cancer Network®

NCCN

# Prevention and Treatment of Cancer-Related Infections, Version 2.2016

## Clinical Practice Guidelines in Oncology

Brenda Cooper, MD; Erik R. Dubberke, MD; Ashley Morris Engemann, PharmD, BCOP; Alison G. Freifeld, MD; John N. Greene, MD; James I. Ito, MD; Daniel R. Kaul, MD; Mark E. Lustberg, MD, PhD; Jose G. Montoya, MD; Ken Rolston, MD; Gowri Satyanarayana, MD; Brahm Segal, MD; Susan K. Seo, MD; Shmuel Shoham, MD; Randy Taplitz, MD; Jeffrey Topal, MD; John W. Wilson, MD; Karin G. Hoffmann, RN, CCM; and Courtney Smith, PhD

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| OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a] | DISEASE/THERAPY EXAMPLES | FEVER & NEUTROPENIA RISK (See FEV-2*) | ANTIMICROBIAL PROPHYLAXIS [d,e,f,g,h,i] |
|---|---|---|---|
| Low | • Standard chemotherapy regimens for most solid tumors<br>• Anticipated neutropenia less than 7 d | Incidence low | • Bacterial - None<br>• Fungal - None<br>• Viral - None unless prior HSV episode |
| Intermediate | • Autologous HCT<br>• Lymphoma[c]<br>• Multiple myeloma[c]<br>• CLL[c]<br>• Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine)<br>• Anticipated neutropenia 7–10 d | Incidence usually high, significant variability may exist | • Bacterial - Consider fluoroquinolone prophylaxis<br>• Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (See INF-2); consider PCP prophylaxis (See INF-6*)<br>• Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5) |
| High[b] | • Allogeneic HCT including cord blood<br>• Acute leukemia<br>▸ Induction<br>▸ Consolidation<br>• Alemtuzumab therapy<br>• GVHD treated with high-dose steroids (>20 mg daily)<br>• Anticipated neutropenia greater than 10 d | Incidence usually high, significant variability may exist | • Bacterial - Consider fluoroquinolone prophylaxis<br>• Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PCP prophylaxis (See INF-6*)<br>• Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5) |

KEY: CLL = chronic lymphocytic leukemia, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, HSV = herpes simplex virus, PCP = *p*neumo*c*ystis *p*neumonia

| OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a] | DISEASE/THERAPY EXAMPLES | ANTIFUNGAL PROPHYLAXIS[f,l] | DURATION |
|---|---|---|---|
| INTERMEDIATE TO HIGH | ALL | Consider:<br>• Fluconazole[m] or Micafungin<br>• Amphotericin B products[n] (category 2B) | Until resolution of neutropenia |
| | MDS (neutropenic)<br><br>AML (neutropenic) | Consider:<br>• Posaconazole[m] (category 1)<br>• Voriconazole[m], Fluconazole[m], Micafungin, or Amphotericin B products[n] (all category 2B) | |
| | Autologous HCT with mucositis[j] | Consider:<br>• Fluconazole[m] or Micafungin (both category 1) | |
| | Autologous HCT without mucositis | Consider no prophylaxis (category 2B) | |
| | Allogeneic HCT (neutropenic)<br>See Antipneumocystis Prophylaxis (INF-6*) | Consider:<br>• Fluconazole[m] or Micafungin (both category 1)<br>• Voriconazole[m], Posaconazole[m], or Amphotericin B product[n] (all category 2B) | Continue during neutropenia and for at least 75 d after transplant |
| | Significant GVHD[k]<br>See Antipneumocystis Prophylaxis (INF-6*) | Consider:<br>• Posaconazole[m] (category 1)<br>• Voriconazole[m], Echinocandin, Amphotericin B products[n] (all category 2B) | Until resolution of significant GVHD |

# Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update Summary

*Randy A. Taplitz, Erin B. Kennedy, and Christopher R. Flowers*

**Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Im**
**Clinical Practice Guideline Update Summary**
Volume

*Recommendation 2.1* Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients at risk for profound, protracted neutropenia (eg, most patients with AML/MDS or HSCT). Antifungal prophylaxis is not routinely recommended for patients with solid tumors. Further distinctions between recommendations for invasive candidiasis and invasive mold infection are provided within the full text of the guideline. (Type of recommendation: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

GUIDELINE ARTICLE

# ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

Frederic Tissot,[1] Sam
Andreas H. Groll,[5] An
Claudio Viscoli[8] and

EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

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Journal of Antimicrobial Chemotherapy

# European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia

Johan A. Maertens[1*], Corrado Girmenia[2], Roger J. Brüggemann[3], Rafael F. Duarte[4], Christopher C. Kibbler[5], Per Ljungman[6], Zdeněk Racil[7], Patricia Ribaud[8], Monica A. Slavin[9,10], Oliver A. Cornely[11–13], J. Peter Donnelly[14] and Catherine Cordonnier[15,16] on behalf of the European Conference on Infections in Leukaemia (ECIL)†, a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and the European LeukemiaNet (ELN)

**Table 3.** ECIL recommendations on primary antifungal prophylaxis in adult patients with AML and MDS undergoing intensive remission-induction chemotherapy[a]

| Antifungal agent | Grading | Comments |
|---|---|---|
| Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1 | A-I | Recommended if baseline incidence of mould infections is high.<br>Given the increased absorption of the tablet, it is likely that the need for therapeutic drug monitoring will become restricted to specific populations (e.g. severe mucositis). |
| Fluconazole 400 mg q24h | B-I | Only recommended if the incidence of mould infections is low.<br>Fluconazole may be part of an integrated care strategy together with a mould-directed diagnostic approach. |
| Itraconazole oral solution 2.5 mg/kg q12h | B-I | Recommended if baseline incidence of mould infections is high.<br>May be limited by drug–drug interactions or patient tolerability.<br>It is recommended to monitor serum drug concentrations. |
| Voriconazole 200 mg q12h | B-II | Recommended if baseline incidence of mould infections is high.<br>It is recommended to monitor serum drug concentrations. |
| All echinocandins | C-II | Insufficient data on efficacy and tolerability. |
| Liposomal amphotericin B | C-II | Insufficient data on dose, frequency and duration, as well as on efficacy and tolerability. |
| Lipid-associated amphotericin B | C-II | Insufficient data on dose, frequency and duration, as well as on efficacy and tolerability. |
| Aerosolized liposomal amphotericin B (10 mg twice weekly) | B-I | Only when combined with fluconazole 400 mg q24h. |
| Amphotericin B deoxycholate | A-II against | |
| Aerosolized amphotericin B deoxycholate | A-I against | |

[a]Primary antifungal prophylaxis might be considered during intensified consolidation therapy (see text).

**Table 4.** ECIL recommendations on primary antifungal prophylaxis in adult allogeneic HSCT recipients: pre-engraftment period

| | Pre-engraftment risk of mould infections | |
|---|---|---|
| Antifungal agent | low | high |
| Fluconazole 400 mg q24h | A-I | |
| Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1 | B-II | B-II |
| Itraconazole oral solution 2.5 mg/kg q12h | B-I | B-I |
| Voriconazole 200 mg q12h | B-I | B-I |
| Micafungin 50 mg q24h | B-I | C-I |
| Caspofungin and anidulafungin | no data | no data |
| Liposomal amphotericin B | C-II | C-II |
| Aerosolized liposomal amphotericin B (10 mg twice weekly) plus fluconazole 400 mg q24h | C-III | B-II |
| Fluconazole 400 mg q24h | | A-III against |

**Table 5.** ECIL recommendations on primary antifungal prophylaxis in adult allogeneic HSCT recipients: post-engraftment period

| Antifungal agent | High risk GvHD |
|---|---|
| Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1 | A-I[a,b] |
| Itraconazole oral solution 2.5 mg/kg q12h | B-I[b] |
| Voriconazole 200 mg q12h | B-I[b] |
| Micafungin 50 mg q24h | C-II |
| Caspofungin and anidulafungin | no data |
| Liposomal amphotericin B | C-II |
| Aerosolized liposomal amphotericin B (10 mg twice weekly) plus fluconazole 400 mg q24h | no data |
| Fluconazole 400 mg q24h | A-III against |

[a]No difference with placebo was seen in patients with chronic GvHD.[59]
[b]It is recommended to monitor serum drug concentrations.

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REVIEW

# Current status of glucocorticoid usage in solid organ transplantation

Simin Dashti-Khavidaki, Reza Saidi, Hong Lu

## ADVANTAGES OF GCs IN SOT

GCs are administered pre-transplant to potential donors and organ perfusate solution to decrease IRI and preserve organs quality; moreover, GCs are given peri- and post-transplant to recipients as induction or maintenance immunosuppression, treatment of acute rejection, or for management of some post-transplant complications.

İki yönlü fayda :
-Hem grefti: İskemi Reperfüzyon
-Hem de alıcıyı: Rejekt

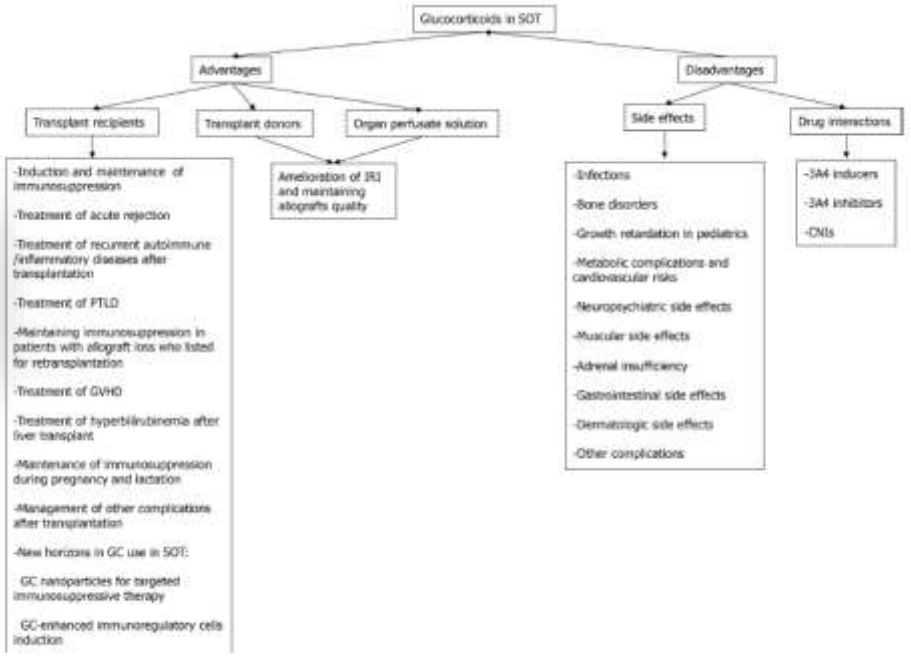


**Figure 1 Advantages and disadvantages of glucocorticoids in solid organ transplantation.** CNI: Calcineurin inhibitor; GC: Glucocorticoid; GVHD: Graft vs host disease; IRI: Ischemia-reperfusion injury; PTLD: Post-transplant lymphoproliferative disorder; SOT: Solid organ transplantation.

**Table 1 Effect of pretreatment of transplant donors with methylprednisolone on outcomes of solid organ transplantation**

| Type of the study | Type of SOT | Follow-up duration | Findings |
|---|---|---|---|
| RCT[57] | Liver | 6 mo | Significant lower liver enzymes in GC *vs* placebo group at 1st and 10th d after transplantation; No difference in PNF rate between groups (2 of 50 patients in GC and 3 of 50 patients in the placebo group); Lower acute rejection during 6 mo in GC group (22% *vs* 36%; $P < 0.05$) |
| RCT[60] | Liver | Maximum 3 yr | No difference in liver enzymes between GC and placebo groups during 1st wk after transplantation; Acute rejection during 3 mo after transplantation was 24% in each group; 1 yr graft loss of 15% in GC and 24% in the placebo group ($P = 0.41$); Relative risk of acute rejection in GC *vs* placebo group: 1.02 (95%CI: 0.5-2.1; $P = 1$); Relative risk of mortality in GC *vs* placebo group: 0.63 (95%CI: 0.29-1.36; $P = 0.31$) |
| Meta-analysis of two above RCTs[61] | Liver | Maximum 6 mo | Risk ratio for incidence of acute rejection during 1 mo to 6 mo after transplantation: 0.72 (95%CI: 0.44-1.19; $P = 0.2$) |
| RCT[59] | Kidney | 5 yr | 3 mo BPAR: 10% in GC and 12% in placebo group ($P = 0.468$); 5 yr graft survival: 84% in GC and 82% in placebo group ($P = 0.941$); Mean eGFR at 5 yr: 47 mL/min/1.73 $m^2$ in GC and 48 mL/min/1.73 $m^2$ in placebo group ($P = 0.756$) |


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Review Article on Strategies to Achieve Long-Term Success of Lung Transplantation



# Infection prophylaxis and management of fungal infections in lung transplant

Armelle Pérez-Cortés Villalobos, Shahid Husain

*Ann Transl Med* 2020;8(6):414

**Table 1** Risk factors for development of IFI's in lung transplant recipients (6,8)

| |
|---|
| Single lung transplant |
| Early airway ischemia |
| CMV infection |
| Rejection and augmented immunosuppression |
| Pre- or post-transplant *Aspergillus* colonization within a year after transplantation |
| Hypogammaglobulinemia (IgG <400 mg/dL) |

**Table 2** Fungal pathogens in lung transplant recipients (14,18,19)

| Pathogen | Usual clinical manifestation |
|---|---|
| *Aspergillus* spp. | Tracheobronchitis; pulmonary disease; extrapulmonary disease |
| *Fusarium* spp. | Skin and soft tissue infection; pulmonary disease; extrapulmonary disease |
| *Scedosporium* spp. | Pulmonary disease; disseminated disease |
| *Candida* spp. | Anastomotic fungal infection; Candidemia |
| *Cryptococcus neoformans* | Pulmonary disease; meningitis; disseminated disease |
| Dematiaceous molds: *Exophiala*, *Alternaria*, *Curvularia*, *Dactylaria*, *Cladophialophora* and others | Skin and soft tissue infection; brain abscess |
| Endemic mycosis: *Blastomycosis*; *Coccidioidomycosis*; *Histoplasmosis* | Fever unknown origin; pulmonary disease; disseminated disease |
| Zygomycetes | Pulmonary disease; rhinocerebral infection; disseminated disease |

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]

**Table 1** Epidemiology of invasive aspergillosis in SOT r
The large variations of the overall mortality rates in hea
kidney recipients can be explained by the correspondi
variations in follow-up in the different studies (3-month
or 12-months [6, 7])

| Population | Incidence (%) | Overall mortality (%) | R |
|---|---|---|---|
| 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 | [ |

**Table 3** Primary antifungal treatment options for the treatment of IA and special considerations in solid organ transplant recipients

| Agent | Dose | Recommendation | Potential Adverse Events | Potential Drug Interactions | Additional Considerations | Monitoring |
|---|---|---|---|---|---|---|
| Voriconazole | Induction: 6 mg/kg IV[a] every 12 h the first day<br>Maintenance: 4 mg/kg IV[a], 200-300 mg PO twice daily | 1st line [14] | -Hepatotoxicity[b]<br>-Visual changes<br>-Neurologic toxicity<br>-Rash and photosensitivity<br>-Periostitis<br>-QTc prolongation[c] | -Sirolimus[d]<br>-Tacrolimus[d]<br>-Cyclosporine[d] | -Non-linear pharmacokinetics<br>-Strong inhibitor of CYP3A4<br>-Moderate inhibitor of CYP2C19 and 2C9<br>-Metabolized via CYP2C19, 2C9 and 3A4<br>- < 2% of voriconazole is excreted in the urine | -Liver function tests<br>-12-lead ECG[c]<br>-Voriconazole TDM[d]<br>-Sirolimus, tacrolimus, and cyclosporine TDM[d] |
| Isavuconazole | Induction: 200 mg three times daily the first 2 days<br>Maintenance: 200 mg daily | 1st line [15]<br>Primary alternative [14] | -Hepatotoxicity[b] | -Sirolimus[e]<br>-Tacrolimus[e]<br>-Cyclosporine[e] | -Linear pharmacokinetics<br>-Moderate inhibitor of CYP3A4<br>-Metabolized via CYP3A4<br>-Isavuconazole may cause QTc shortening | -Liver function tests<br>-Sirolimus, tacrolimus, and cyclosporine TDM[e] |
| Liposomal Amphotericin B | 3–5 mg/kg daily IV | Primary alternative [14, 15] | - Nephrotoxicity[g] | | | -Renal function and electrolytes |

**Table 3** Preventive strategies with antifungals in lung transplant recipients (20,30,46-48)

| Strategy | Recommendation | Prophylaxis |
|---|---|---|
| Universal prophylaxis | To all patients during the immediate post-transplant period | |
| Targeted antifungal prophylaxis | In patients with any of the following risk factors: single lung transplant, early airway ischemia, rejection or change immunosuppression, pre-transplant colonization, induction with alemtuzumab or anti-thymocyte globulin, positive intraoperative *Aspergillus* culture in CF patient, hypogammaglobulinemia, CMV infection; and that will be followed with BAL cultures and BAL galactomannan | Nebulized L-Amb; voriconazole; posaconazole; isavuconazole; usually for 4–6 months |
| Preemptive therapy | Administration of antifungal agents for molds isolated during surveillance post-transplant bronchoscopy without evidence of invasive disease | Depends on the mold isolated |

**Table 4** Complications after fungal invasive infections in lung transplant recipients

| Complications | Mortality | Association with clad |
|---|---|---|
| Invasive aspergillosis | 58% after 2-year post-lung transplant (50) | Reported (55-57) |
| Scedosporiosis | In SOT was 54% (31 of 57) (47); 77.8% *S. prolificans* infection; 54.5% *S. apiospermum* infection | Reported (58) |
| Cryptococcosis | In SOT population ranges from 14–19.6% (52,53) | |
| Candidiasis | In SOT population 54% (6 of 11) (12) | |
| Fusariosis | In lung transplant recipients 67% (54) | |

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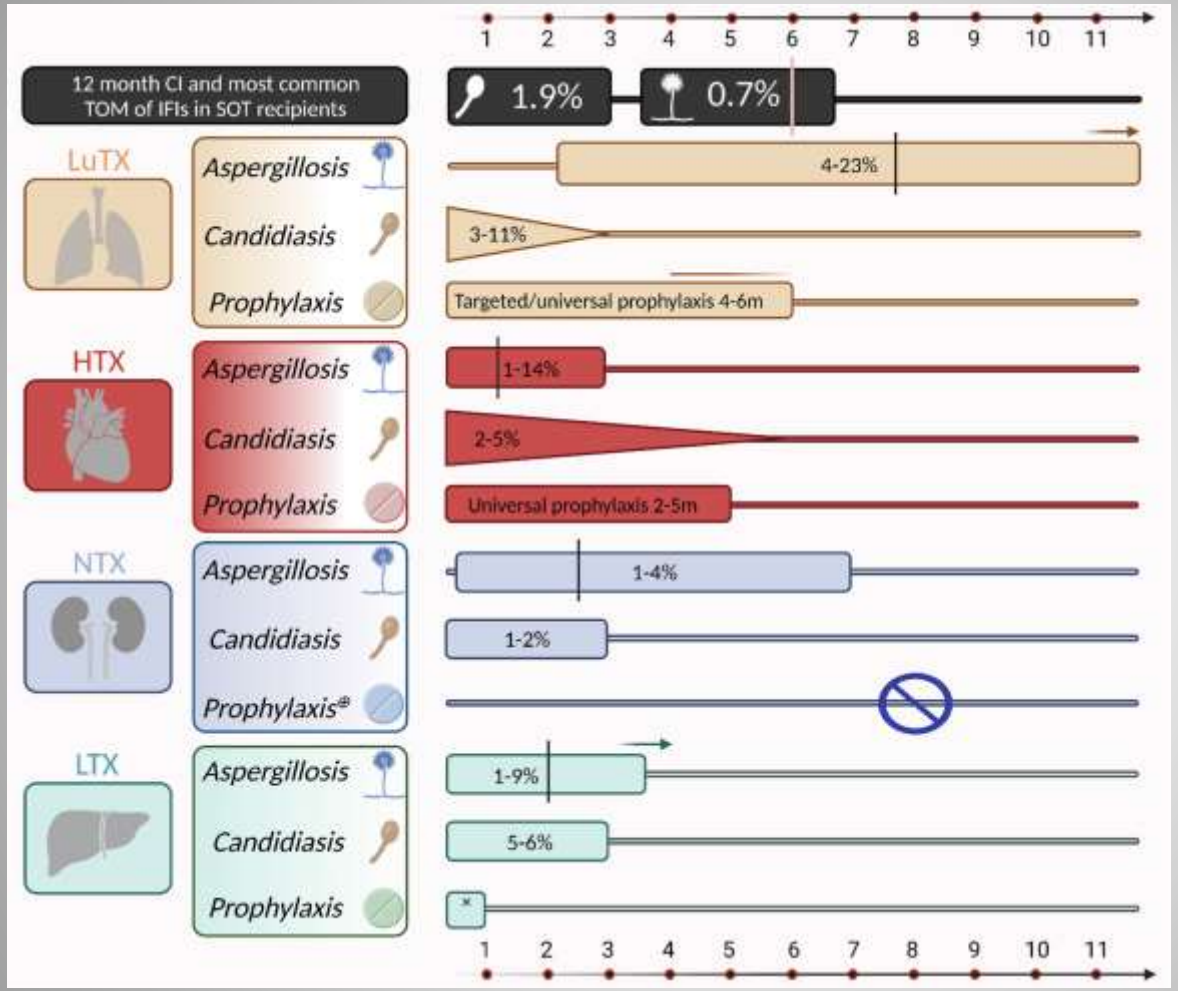


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**Observations and Research**

CROHN'S & COLITIS FOUNDATION

# Corticosteroids Increase the Risk of Invasive Fungal Infections More Than Tumor Necrosis Factor-Alpha Inhibitors in Patients With Inflammatory Bowel Disease

**Martin H. Gregory, MD, MSCI,* Andrej Spec, MD, MSCI,† Dustin Stwalley, MA,‡ Anas Gremida, MD,* Carlos Mejia-Chew, MD,† Katelin B. Nickel, MPH,† Matthew A. Ciorba, MD,* Richard P. Rood, MD,* Margaret A. Olsen, PhD, MPH,† and Parakkal Deepak, MBBS, MS***

*Inflammatory Bowel Diseases Center, Division of Gastroenterology, Washington University School of Medicine, Saint Louis, Missouri, USA
†Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri, USA
‡Institute for Informatics, Washington University School of Medicine, Saint Louis, Missouri, USA

Address correspondence to: Martin H. Gregory, MD, MSCI, Inflammatory Bowel Diseases Center, Division of Gastroenterology, Washington University School of Medicine, 600 South Euclid Avenue, MSC 8124-21-427, Saint Louis, MO 63110, USA (martingregory@wustl.edu).

2006-2018 retrospektif
Ayaktan+ Yatan
652.920 İBH
-291.506 CH ve 353.165 ÜK
%50 GK

**TNFα-inhibitörleri:**
Adalimumab
İnfliximab
Certolizumab pegol
Golimumab
Vedolimumab
Ustekinumab

**Table 2.** Organisms causing invasive fungal infections in patients with inflammatory bowel disease.

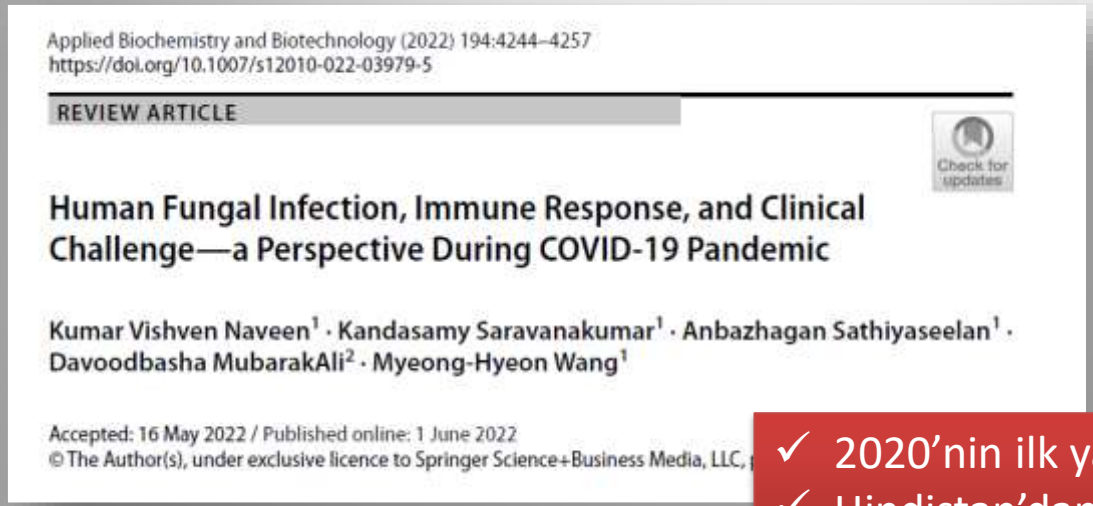
| | Cases (*N*, %) | Rate (cases/100 000 person-years) | 95% lower CI | 95% upper CI |
|---|---|---|---|---|
| Invasive fungal infection | 775 (100) | 47.93 | 44.67 | 51.42 |
| Histoplasmosis | 194 (25.03) | 11.99 | 10.41 | 13.80 |
| Invasive candidiasis | 150 (19.35) | 9.27 | 7.90 | 10.88 |
| Coccidiomycosis | 142 (18.32) | 8.77 | 7.44 | 10.34 |
| Aspergillus | 119 (15.35) | 7.35 | 6.14 | 8.80 |
| *Pneumocystis jiroveci* | 81 (10.45) | 5.00 | 4.03 | 6.22 |
| Cryptococcus | 46 (5.94) | 2.84 | 2.13 | 3.79 |
| Blastomycosis | 12 (1.55) | 0.74 | 0.42 | 1.31 |
| Fungal pneumonia | 20 (2.58) | 1.24 | 0.79 | 1.92 |
| Mucormycosis | 6 (0.77) | 0.37 | 0.17 | 0.83 |
| Fungal meningitis | 3 (0.39) | 0.19 | 0.06 | 0.57 |
| Paracoccidiomycosis | 2 (0.26) | 0.12 | 0.03 | 0.49 |

**Table 3.** Hazard ratios from a Cox proportional hazards model for risk of invasive fungal infections in patients with inflammatory bowel disease including immunomodulators.

| | Hazard ratio | 95% lower | 95% upper | *P* |
|---|---|---|---|---|
| Anti-TNF monotherapy[a] | 2.486 | 1.691 | 3.653 | <.0001 |
| Corticosteroids only[a] | 5.655 | 4.764 | 6.714 | <.0001 |
| Immunomodulator monotherapy[a,b] | 1.099 | 0.749 | 1.614 | .6294 |
| Anti-TNF + immunomodulator[a,b] | 1.648 | 0.733 | 3.704 | .2268 |
| Immunomodulator + corticosteroids | 6.012 | 4.550 | 7.943 | <.0001 |
| Anti-TNF + corticosteroids[a,b] | 8.100 | 5.679 | 11.551 | <.0001 |
| Anti-TNF + immunomodulator + corticosteroids[a,b] | 6.628 | 3.790 | 11.591 | <.0001 |

# Yeni ama eski risk…

- COVID-19 (Viral solunum yolu infeksiyonları)



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REVIEW ARTICLE

Check for updates

**Human Fungal Infection, Immune Response, and Clinical Challenge—a Perspective During COVID-19 Pandemic**

Kumar Vishven Naveen[1] · Kandasamy Saravanakumar[1] · Anbazhagan Sathiyaseelan[1] · Davoodbasha MubarakAli[2] · Myeong-Hyeon Wang[1]

Accepted: 16 May 2022 / Published online: 1 June 2022


- ✓ 2020'nin ilk yarısında Çin'den Aspergillosis
- ✓ Hindistan'dan 14.000 vakalık «kara mantar» mukormikoz bildirimi

Wang J. *Critical Care, 2020. 24*, 299
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**Table 1** Characteristics of COVID-19 patients with co-fungal infections

| Country | COVID-19 patients (no.) | Age (years) | Secondary fungal infection (%) | Mortality (%) | Fungal isolate | Reference |
|---|---|---|---|---|---|---|
| Italy | 108 | 63 (median) | 27.7 | 44 | *Aspergillus* sp. | Bartoletti et al. 2020 |
| Belgium | 34 | 66 | 20.5 | 58.8 | *A. flavus, A. fumigatus* | Rutsaert et al. 2020 |
| England | 135 | 57 (median) | 18.5 | 52 | *Aspergillus* sp. | White et al. 2020 |
| Netherlands | 42 | 68 (mean) | 21.4 | 22.2 | *Aspergillus* sp. | Van Biesen et al. 2020 |
| France | 27 | 63 | 33.3 | 44.4 | *A. fumigatus* | Alanio et al. 2020 |
| Pakistan | 147 | 71 (median) | 6.1 | 60 | *A. flavus, A. fumigatus, A. niger* | Nasir et al. 2020 |
| China | 52 | ND | 5.8 | ND | *A. flavus, A. fumigatus, C. albicans* | Yang et al. 2020 |
| USA | 41 | 54 (median) | 100 | 48.7 | Black fungus | Agnihotri et al. 2021 |
| India | 40,805 | ND | 100 | 7.66 | Black fungus | Rahman et al. 2021 |

Fungal PAMPs x TLR-2; TLR-4; TLR-9; NLRs….
Sinerji…
Sitokin fırtınasında artış…

COVID-19'un neden olduğu hipoksi

**Table 2** Summary of the clinical characteristics of the COVID-19 patients with secondary fungal infections and utilized anti-inflammatory drugs and antifungal medications during the treatments

| Symptoms/complications | COVID-19 treatment/steroid therapy | Secondary fungal infection | Antifungal used | Reference |
|---|---|---|---|---|
| Acute pulmonary embolism, bacterial pneumonia | Meropenem, levofloxacin, trimethoprim/sulfamethoxazole, amikacin, tigecycline, colistin | Candidemia | Intravenous fluconazole | (3) |
| Diabetes, heart disease, bacterial superinfection | Darunavir/ritonavir, hydroxychloroquine, piperacillin/tazobactam, teicoplanin, ertapenem, colistin | Candidemia | Caspofungin | (25) |
| Diabetes, cardiovascular disorder | Hydroxychloroquine | Aspergillosis | Azoles, liposomal amphotericin B | (2) |
| Chronic respiratory disease | Prednisolone, methylprednisolone, hydrocortisone, dexamethasone, and fludrocortisone | Aspergillosis, yeast infections | ND | (40) |
| HIV-positive | Tenofovir/lamivudine and atazanavir/ritonavir ceftriaxone, azithromycin, dexamethasone, emtricitabine | Histoplasmosis | Itraconazole, amphotericin B deoxycholate | (4) |
| ND | Remdesivir, dexamethasone, metformin, glipizide | Mucormycosis | Amphotericin B, ceftriaxone | (36) |
| Diabetes | Remdesivir, ceftriaxone, azithromycin, dexamethasone | Mucormycosis | Voriconazole, liposomal amphotericin B | (13) |
| Diabetes | Corticosteroids | Mucormycosis | Liposomal amphotericin B, voriconazole, posaconazole | (20) |

- COVID-19 yönetiminde kullandığımız glukokortikoidler ve/veya immünmodülatör ajanlar hastalık için hayati önem taşır

- Fungal infeksiyonlar üzerine olan etkileri ile değerlendirildiğinde ise daha büyük problemlere yol açar
  - Hastalığın seyri
  - Antifungal kullanımında artış
  - Antifungal direcinde artış

- İki yüzü keskin bıçak

# Sonuç:

- Bariyer-Giriş Önlemleri etkili

- Hematolojik malignitelerde profilaksi net…
  - Hastalık
  - Tedavi
- Romatolojik/otoinflamatuvar hastalıklarda işler karışık!!!
  - Tedavi ile hastalık zıt etkili

- Türkiye gerçeği SUT…

Bir yer var, biliyorum;

Her şeyi söylemek mümkün;

Epeyce yaklaşmışım, duyuyorum;

Anlatamıyorum.

*Orhan Veli Kanık*

***Teşekkürler…***