İnvazif Aspergillus Olgusunda Multidisipliner Yolculuk: Tanıdan Tedaviye Zorlu Süreç

Giriş ve Epidemiyoloji

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Enfeksiyon Hast ve Kl Mik

İnvaziv Fungal Enfeksiyonlar

- Maya
  - Kandidiyaz
  - Kriptokok
- Küf
  - Aspergillus
  - Mukormikoz
  - Non-Aspergillus Hyalohyphomycetes (Fusarium, Scedosporium, Lomentospora)
  - Phaeohyphomycetes (Alternaria, Bipolaris, Curvularia, Cladosporium, Exserohilum spp)
- *Pneumocystis jirovecii*
- Endemik mikozlar

İnvaziv Küf Enfeksiyonları

- 14 ⟶ 27.2 /100.000 hasta/yıl son 25 yılda
- Mortalite %25-50
- Antifungal direnç durumlarında mortalite %80

Giannella M et al. Invasive fungal disease in the immunocompromised host: changing epidemiology, new antifungal therapies, and management challenges. Clin Microbiol Infect. 2025.
Apostolopoulou A et al.The changing epidemiology of invasive mold diseases in immunosuppressed patients: what, why, how? Clin Microbiol Infect. 2025.

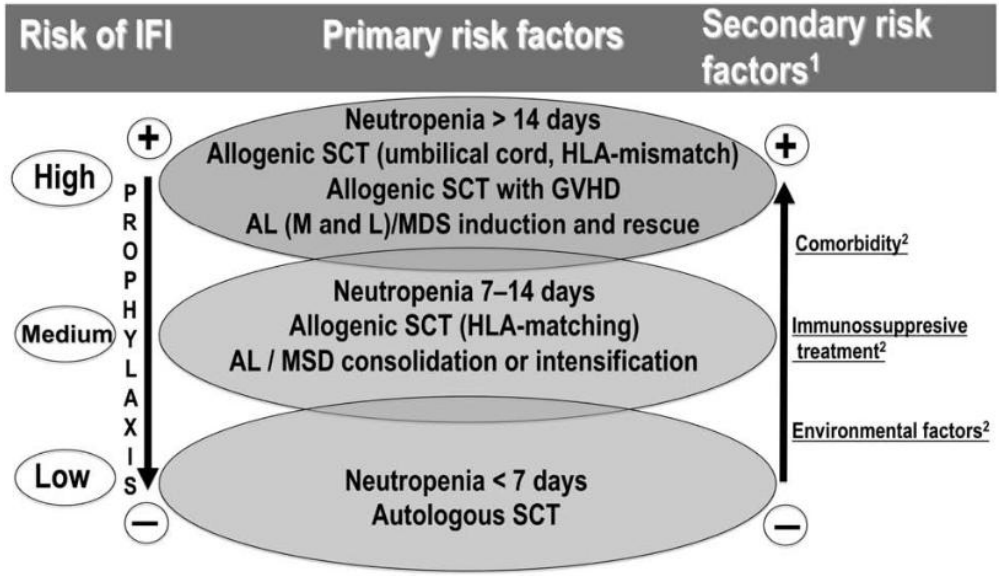
Aspergillus'ta Değişen Epidemiyoloji

- Azol kullanımında artış
- Küf enfeksiyonlarının tanımına yönelik konsensusların sağlanması
- Klinik pratiğe giren fungal biomarkerlar ve moleküler tanı testleri
- COVID-19 pandemisi

Apostolopoulou A, Kampouri E, Little JS, The changing epidemiology of invasive mold diseases in immunosuppressed patients: what, why, how?, Clinical Microbiology and Infection

Aspergillus'ta Değişen Epidemiyoloji

- **Değişen konak faktörleri**
  - Nakil sayısında artış
  - Geleneksel risk faktörleri (nötropeni, steroid kullanımı, hematolojik malignite, HKHN)



Apostolopoulou A, Kampouri E, Little JS, The changing epidemiology of invasive mold diseases in immunosuppressed patients: what, why, how?, Clinical Microbiology and Infection

Barberán José et al. Recommendations for the treatment of invasive fungal infection caused by filamentous fungi in the hematological patient. *Rev Esp Quimioter*. 2011;24(4):263-70.

Aspergillus'ta Değişen Epidemiyoloji

- **Değişen konak faktörleri**
  - Yeni risk faktörleri (kombinasyon tedavileri, hücresel tedaviler, bispesifik ve trispesifik antikor tedavileri, COVID-19 ve influenza ilişkili aspergilloz)
  - Uzamış antifungal profilaksi/tedavi
    - Breaktrough küf enfeksiyonları
    - Azol profilaksisi ile nadir mantar ve azol dirençli mantar enfeksiyonlarında rölatif artış? (dirençli suş seçilimi)
    - Subterapötik antifungal plazma konsantrasyonları

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Aspergillus'ta Değişen Epidemiyoloji

- **Yeni immunoterapiler**
  - 2009-2020 arası 300'den fazla yeni anti-kanser ilaç başvurusu
    - Bruton-kinaz inhibitörleri ile artan invaziv aspergillosis
    - TNF-α inhibitörleri, Janus kinaz inhibitörleri, anti-CD52 inhibitörü (alemtuzumab), blinatumomab gibi bispesifik T hücresi bağlayıcıları ve PI3K inhibitörleri ile artan küf enfeksiyonları (anti-küf profilaksi önerileri henüz net değil)
    - CAR-T hücre tedavisi

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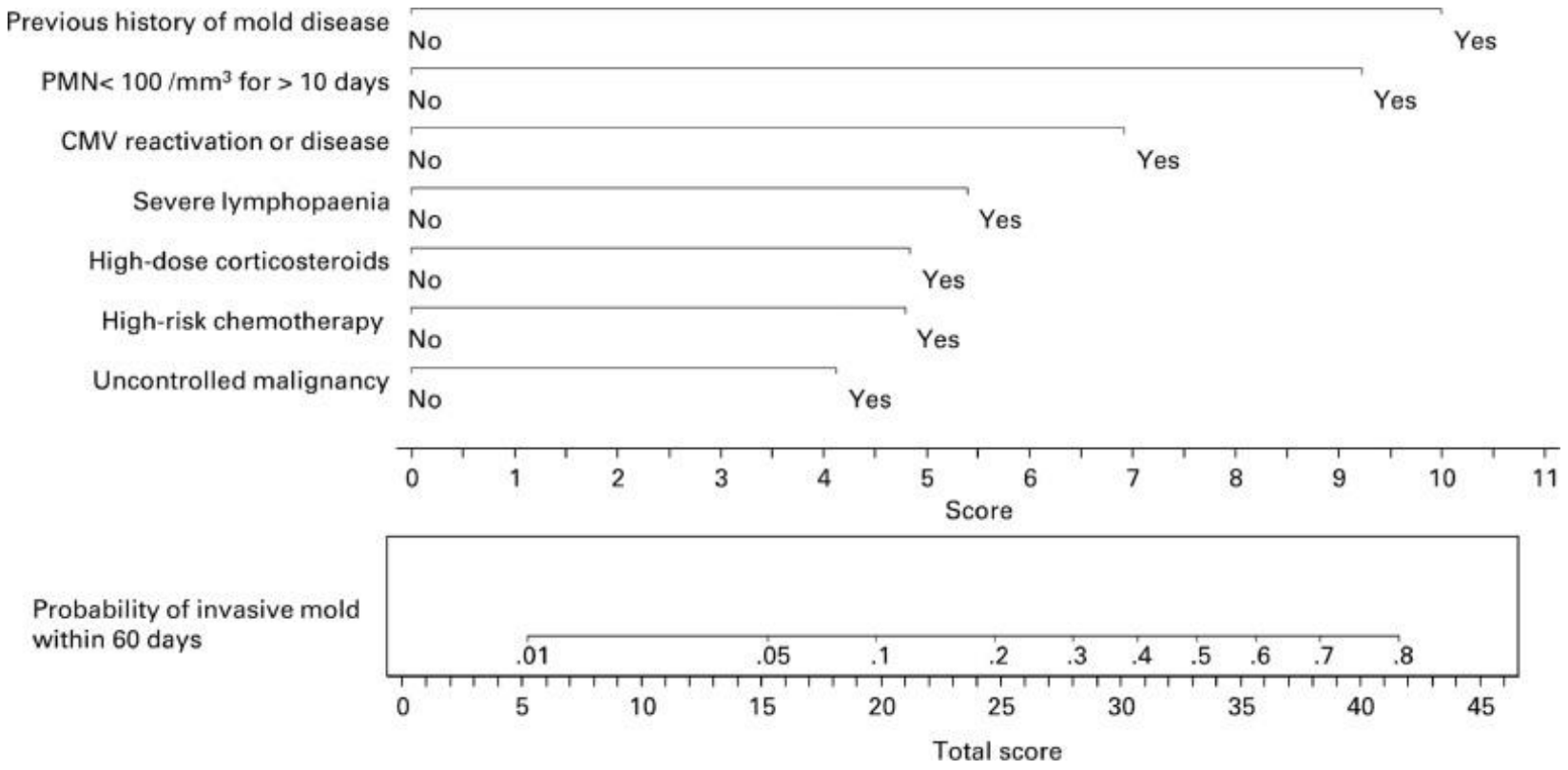
Immunomodulatory Therapies	Immunologic Effects	Association with IMI and level of evidence	Incidence of IFI or IMI if reported
Hematopoietic cell transplantation	Conditioning leads to bone marrow ablation; is followed by engraftment of new donor stem cells and slow reconstitution of immune function	Increased risk of IFI related to prolonged neutropenia and deficits in cell-mediated immunity Large epidemiologic studies (TRANSNET); systematic review and metanalysis	1-year IFI incidence of 5.8 – 8.1% depending on donor type in a large epidemiologic study(1)
Bruton tyrosine kinase (BTK) Inhibitors	Inhibits BTK which plays a key role in B-cell receptor signaling	Increased risk of IA due to impaired neutrophil-mediated damage to Aspergillus Real-world surveillance data, established pathogenesis(2–4)	Incidence of IMI ranges from 3-12%in retrospective studies(5,6) One study in patients with PCNSL reported 39% with diagnosis of IA(4)
Anti-CD52 inhibitor (alemtuzumab)	Binds CD52 triggering lysis and leading to prolonged and profound T and B-cell depletion	Potential increased risk of IMI Retrospective cohort data	Risk depends on underlying disease and indication Reported 11-17% in two retrospective studies of patients with lymphoproliferative disorders(7,8)
CAR T-cell therapy	Lymphodepleting chemotherapy leads to neutropenia. Genetically modified T cells target tumor antigens - off-target immunologic effects depend on targeted antigen	Risk of IMI is relatively low; may be associated with corticosteroid use for acute toxicities Systematic review and metanalyses; retrospective cohort data	Pooled IFI incidence 2-5% in two large systematic reviews and metanalyses(9,10) Proven/probable IMI incidence ~ 1-2% in real-world studies(11–13)
TNF-α Inhibitors (e.g. infliximab, etanercept)	Modulates inflammatory responses, suppresses TNF-mediated T-cell and macrophage activation.	Histoplasmosis > IMI but studies show increased risk of IA Large epidemiologic and database studies	Aspergillosis in 1.3% of patients in a large database study of >33,000 new recipients of TNF-α Inhibitors(14) 1-year IFI incidence <0.5% in a large epidemiologic study using a commercial health insurance claims database(15)
Janus Kinase Inhibitors (e.g. ruxolitinib, tofacitinib)	Reduces cytokine-driven inflammation by inhibiting JAK-STAT pathway, leading to broad immunomodulation.	Potential increased risk of IFI (molds << yeasts, dimorphic fungi) Review of case reports / series(16); further studies needed	Risk depends on underlying disease and indication
PI3K Inhibitors	Mediates B-cell receptor and T-cell receptor signaling involved in cell survival and proliferation.	Potential increased risk of IMI Case reports/series; further studies needed	Unknown; one study showed a lower risk of IFI compared to patients receiving a BTK inhibitor(17)
Bispecific Antibody Therapies	Binds dual antigens (tumor antigen and effector cell [typically CD3 on cytotoxic T cells]) leading to tumor cell death. Off target immunologic effects depend on antigen. Possible T cell exhaustion reported.	Risk of IMI not well described Systematic review data	Unknown; pooled incidence of IFI 6% in one systematic review but primarily *Pneumocystis jirovecii* pneumonia; IMI rare(18)

Hematolojik Maligniteli hastalarda 60 gün İFE risk modellemesi



STANZANI, Marta, et al. Development and internal validation of a model for predicting 60-day risk of invasive mould disease in patients with haematological malignancies. *Journal of Infection*, 2019, 78.6: 484-490.

Teşekkür ederim