SALON A - 19 MAYIS

KURS 5: Febril Nötropeni Kursu (İnvaziv Fungal Enfeksiyonlar Çalışma Grubu)

Moderatörler: **Yasemin Çağ, Ayşegül Ulu Kılıç, Canan Ağalar**

Kurs Programı İçin Tıklayınız

Oturum Başkanları: **Yasemin Çağ, Canan Ağalar**

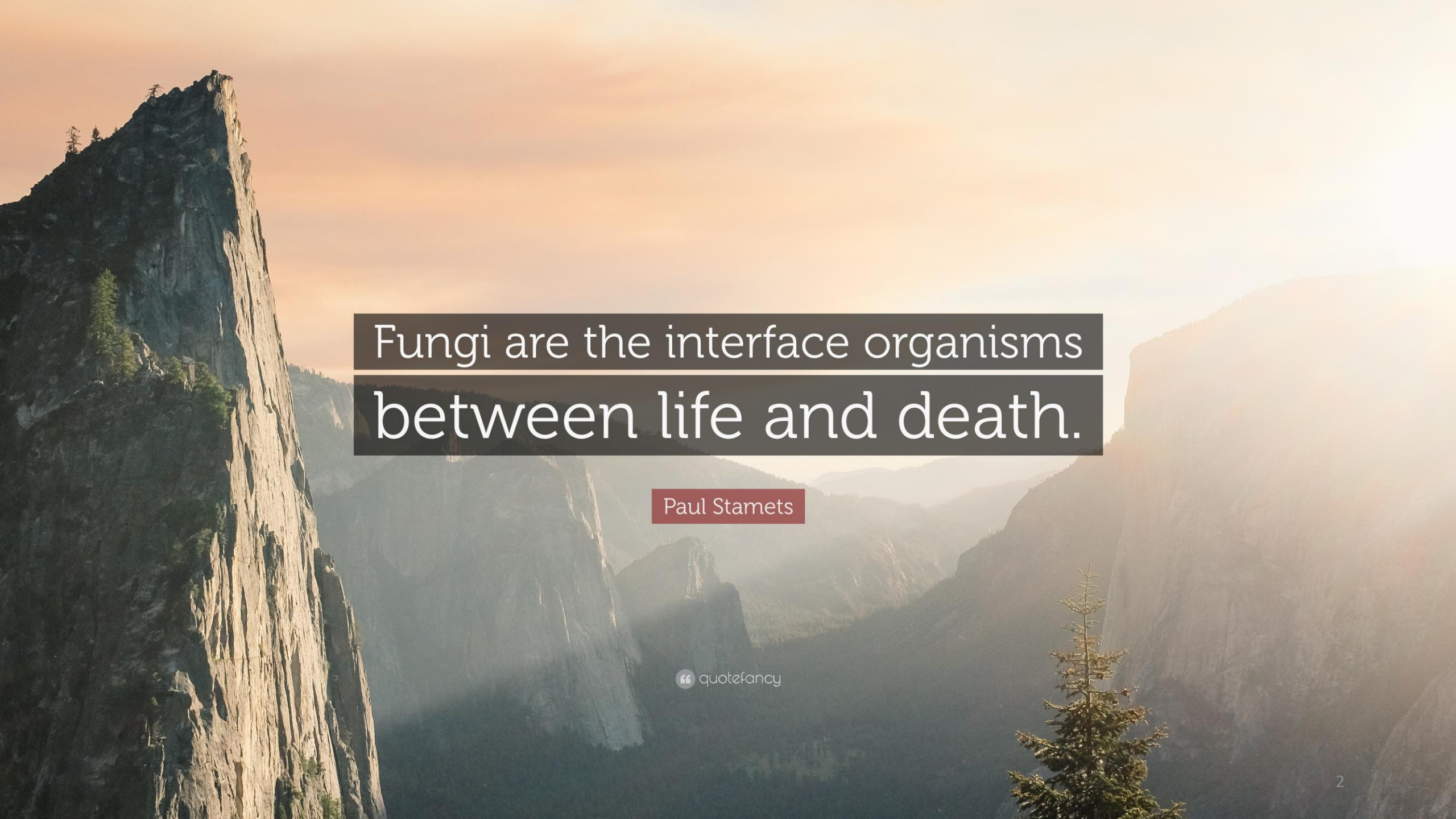
15:30-15:40	**Açılış**
15:40-16:10	Antibakteriyel, Antifungal, Antiviral Profilaksi - **Özlem Güzel Tunçcan**
16:10-16:40	FEN Empirik Antibakteriyel Tedavi Yönetimi - **Hüseyin Aytaç Erdem**
16:40–17:00	Kahve Arası
17:00-18:30	**Fungal Enfeksiyonların Yönetimi** Oturum Başkanları: **Ayşegül Ulu Kılıç, Canan Ağalar**
	İnvaziv Kandidiyazis - **Nagihan Didem Sarı**
	İnvaziv Pulmoner Aspergilloz - **Bilgin Arda**
	Mukormikoz - **Süheyla Kömür**

Mukormikoz

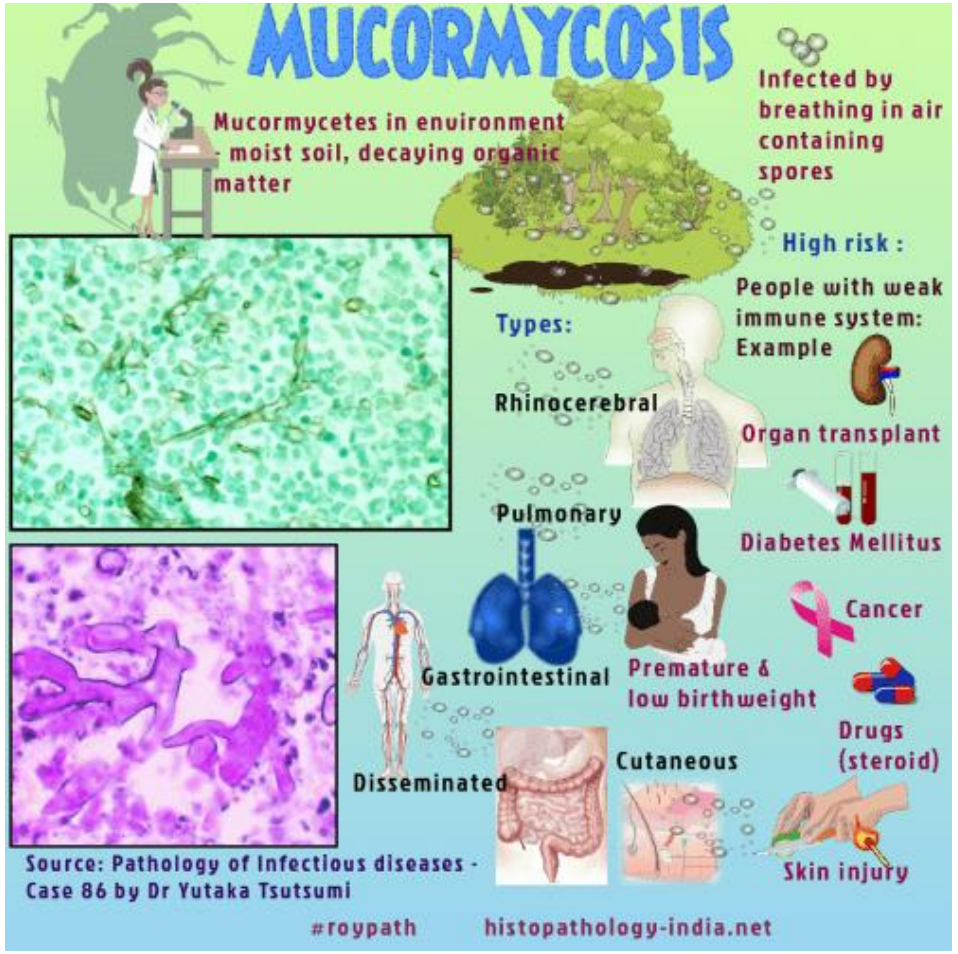
Dr. Süheyla Kömür

ÇÜTF ENFEKSİYON HASTALIKLARI AD

12. TÜRKİYE EKMUD BİLİMSEL KONGRESİ


Fungi are the interface organisms
between life and death.
Paul Stamets
quotefancy

Etken



- Zygomycetes sınıfı ve Mucorales takımı içindeki filamentli küfler
  - *Rhizopus* olguların çoğunda (%70), *Mucor* ve *Lichtheimia*
  - Daha nadir : *Cunninghamella, Apophysomyces, Saksenaea, Rhizomucor, Cokeromyces, Actinomucor, Syncephalastrum*

Alqarihi A, Kontoyiannis DP and Ibrahim AS (2023) Mucormycosis in 2023: an update on pathogenesis and management. Front. Cell. Infect. Microbiol. 13:1254919. doi: 10.3389/fcimb.2023.1254919

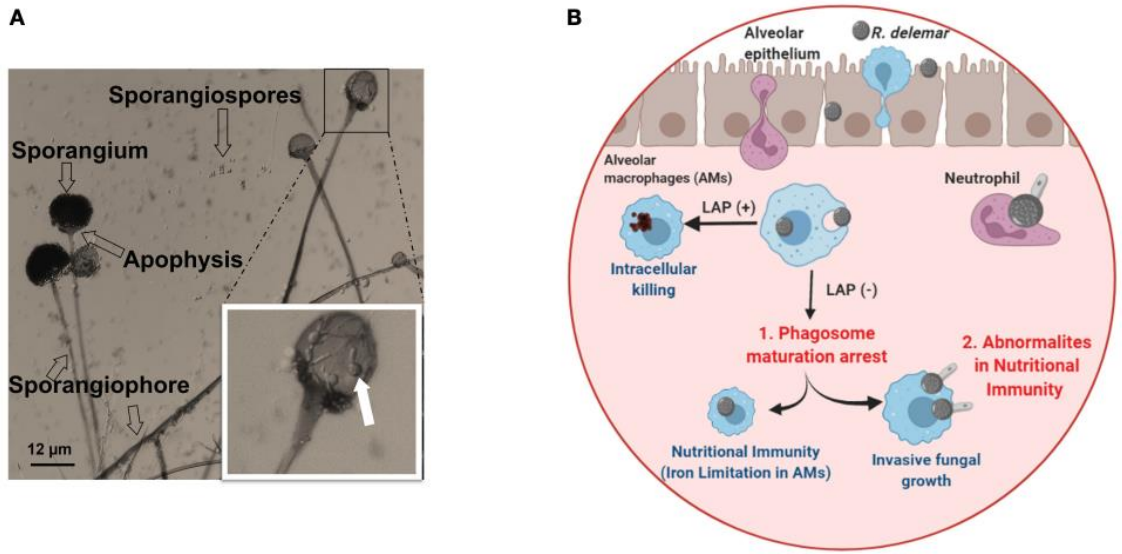


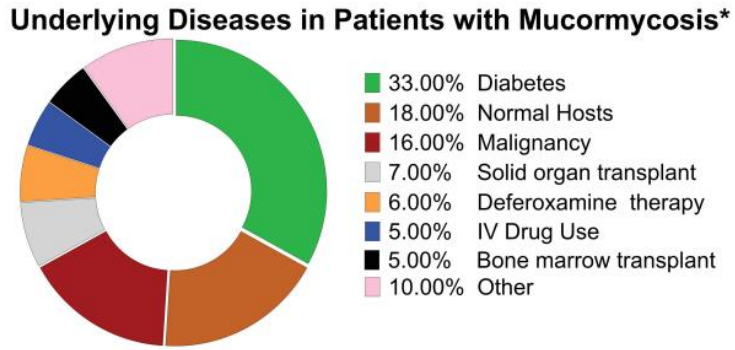
FIGURE 2
(A) Morphology of *Rhizopus delemar*. Sporangia form at the apices of sporangiophores and contain the asexual sporangiospores. Germinated spores seen in the sporangium magnified box can be an overlay of the sporangium on released and germinated spores. **(B)** Under normal circumstance, alveolar macrophages (AMS) are able to phagocytize fungi and killing through LC3-associated phagocytosis (LAP+). While AMS are able to phagocytize Mucorales spores, spore melanin is able to arrest LAP to prevent phagosome maturation. However, spores are unable to grow and germinate due to iron restriction (Frąc et al., 2018). In the presence of abnormal nutritional immunity (*i.e.* excessive iron) spores are able to germinate and kill Ams (Andrianaki et al., 2018). Courtesy of Dr. Georgios Chamilos. "Created with BioRender.com".

Epidemiyoloji

- Son 15 yılda artışta
- Pek çok ülkeden bildirimler mevcut
- Hindistan- COVID-19 pandemisi ile hiperendemik
- 3. sıklıkta invaziv mantar enfeksiyon etkeni
- Transplant ünitelerinde artış
  - Vorikonazol profilaksisi suçlanmakta

Roden et al., 2005
Ambrosioni et al., 2010
Kontoyiannis et al., 2000
Petrikkos et al., 2012

A



B

Microbiological findings for 465 patients with Mucorales*

Organism isolated	No. (%) of all patients
Rhizopus species	218 (47)
Not speciated	125 (27)
R. oryzae	55 (12)
R. rhizopodiformis	20 (4)
R. microsporus	11 (2)
R. Nigricans	7 (2)
R. stolonifer	1 (1)
Mucor species	85 (18)
Cunninghamella bertholletiae	34 (7)
Apophysomyces elegans	27 (6)
Lechtheimia species	25 (5)
Saksenaea species	21 (5)
Rhizomucor pusillus	19 (4)
Entomophthora species	13 (3)
Conidiobolus species	10 (2.2)
Basidiobolus species	9 (2)
Cokeromyces species	3 (0.6)
Syncephalastrum species	1 (0.2)

C

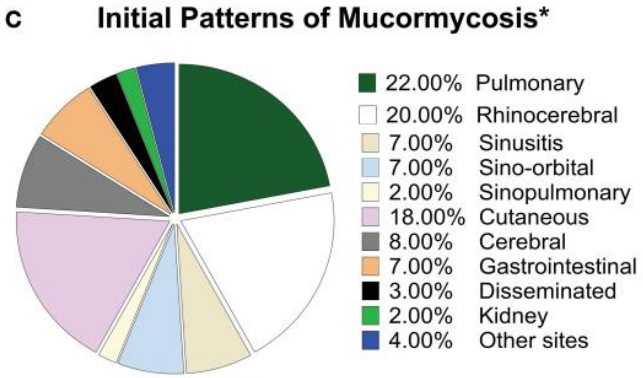


FIGURE 1
Frequency of mucormycosis manifestation in susceptible hosts and the etiologic agents of the disease. **(A)** Frequency of mucormycosis by underlaying predisposing host condition. **(B)** Etiological agents of mucormycosis. **(C)** Frequency of different types of mucormycosis reported.
* Data adapted from Roden M et al. CID 2005 (Roden et al., 2005).

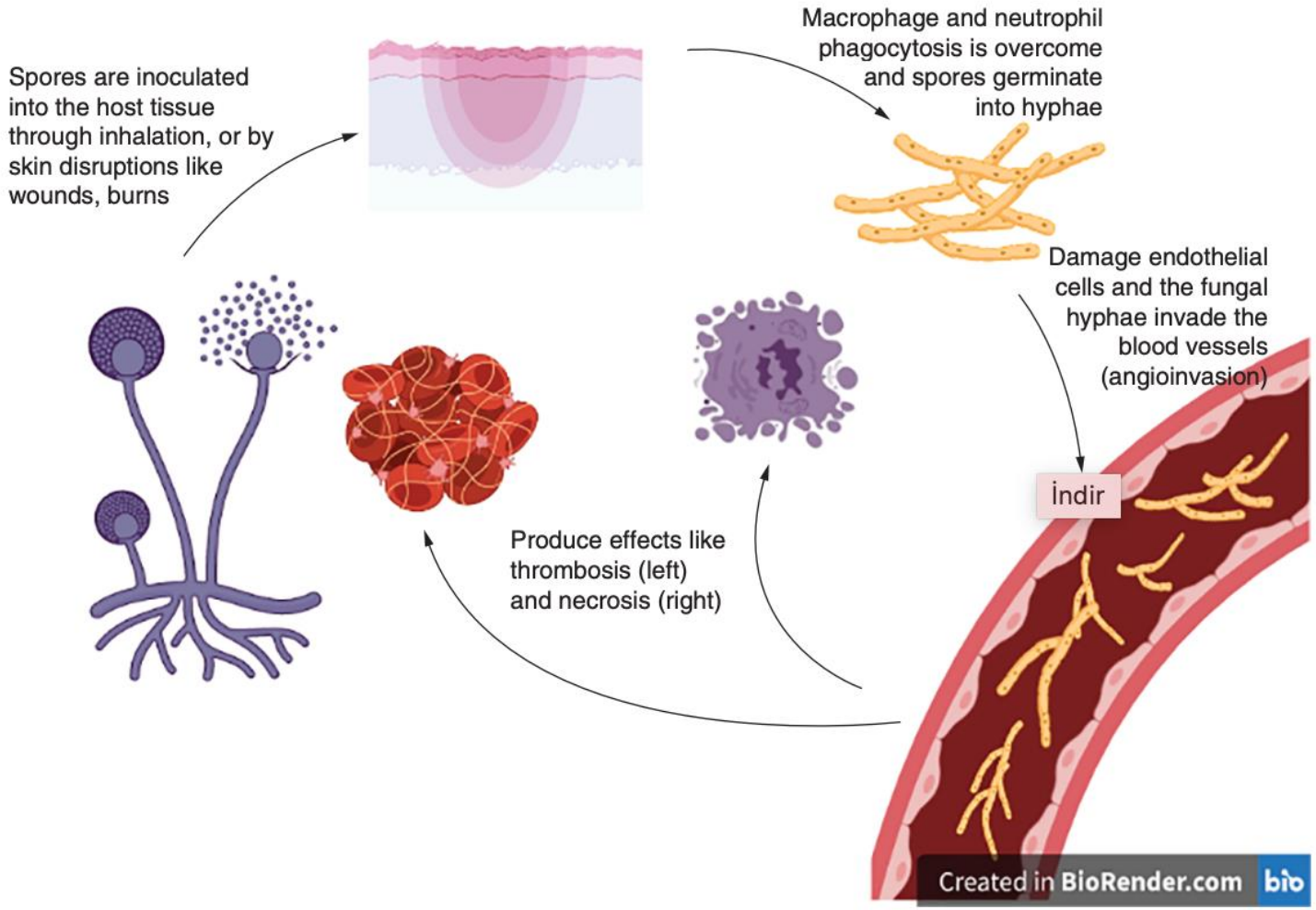


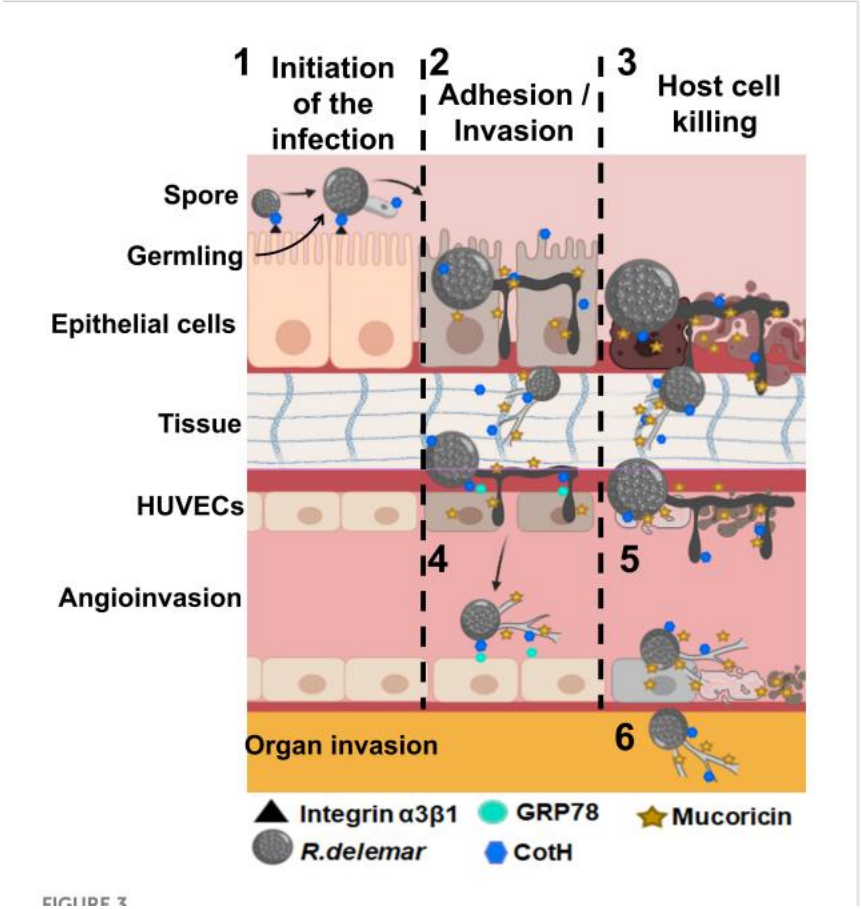
Figure 3. General mechanism of pathogenesis in mucormycosis.
Created with BioRender.com, reference no. 2945-5180.

Konak immün yanıtı

- **Konak bariyer hücreleri**
  - Nazal ve alveoler epitel hücrelere invazyon- GRP78 reseptörü
  - Hematojen yayılma
- **Doğal immünite**
  - Makrofajlar
  - Diyabetik ketoasidoz durumunda makrofajlar fagosite edilmiş Mucorales sporlarını öldürememekte- aspergillus'tan farklı!
- **Adaptif immünite**

Patojenite faktörleri

- Hif/spor oluşumu
- Hızlı morfolojik değişimler
- Demir kullanımı
- Spor coathing proteinler
- Mikotoksinler



Risk faktörleri

- Hematolojik malignite, KHN
- Uzamış/ciddi nötropeni
- Kontrolsüz diabet
- Solid organ kanseri /transplatasyon
- Aşırı demir yüklenmesi, deferoxamin tedavisi
- Uzun süreli vorikonazol kullanımı
- Major travma

  Yanık, penetran travma, cerrahi yara
- Uzamış kortikosteroid kullanımı
- Böbrek yetmezliği
- HIV
- İV ilaç alışkanlığı
- Malnutrisyon
- Prematurite

Klinik Tutulum

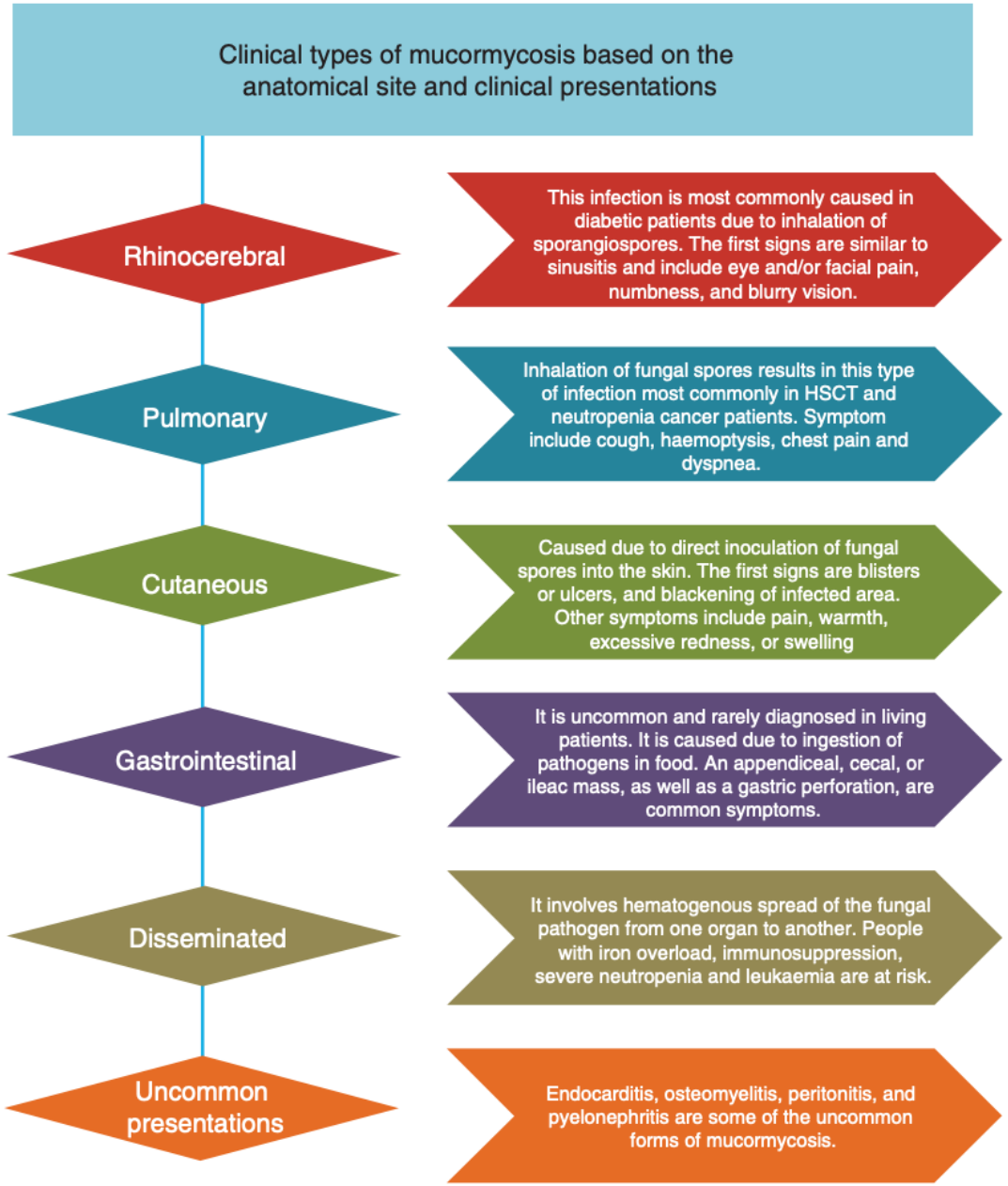


Figure 4. Various clinical types of mucormycosis based on the presentation of symptoms and the anatomical site affected.

Table 1: Warning symptoms and signs of rhino-orbito-cerebral mucormycosis

- Nasal stuffiness
- Foul smell
- Epistaxis
- Nasal discharge - mucoid, purulent, blood-tinged or black
- Nasal mucosal erythema, inflammation, purple or blue discoloration, white ulcer, ischemia, or eschar
- Eyelid, periocular or facial edema
- Eyelid, periocular, facial discoloration
- Regional pain – orbit, paranasal sinus or dental pain
- Facial pain
- Worsening headache
- Proptosis
- Sudden loss of vision
- Facial paresthesia, anesthesia
- Sudden ptosis
- Ocular motility restriction, diplopia
- Facial palsy
- Fever, altered sensorium, paralysis, focal seizures

Tanı

- Klinik şüphe önemli
- + Risk faktörleri:
  - sinüzit, periorbital selülit, fasiyal paralizi, ağız içinde standart tedaviye cevap vermeyen ülser
  - Akciğer grafisinde tedaviye rağmen artan infiltrasyon
  - Yanık veya yara üzerinde siyah renk oluşumu

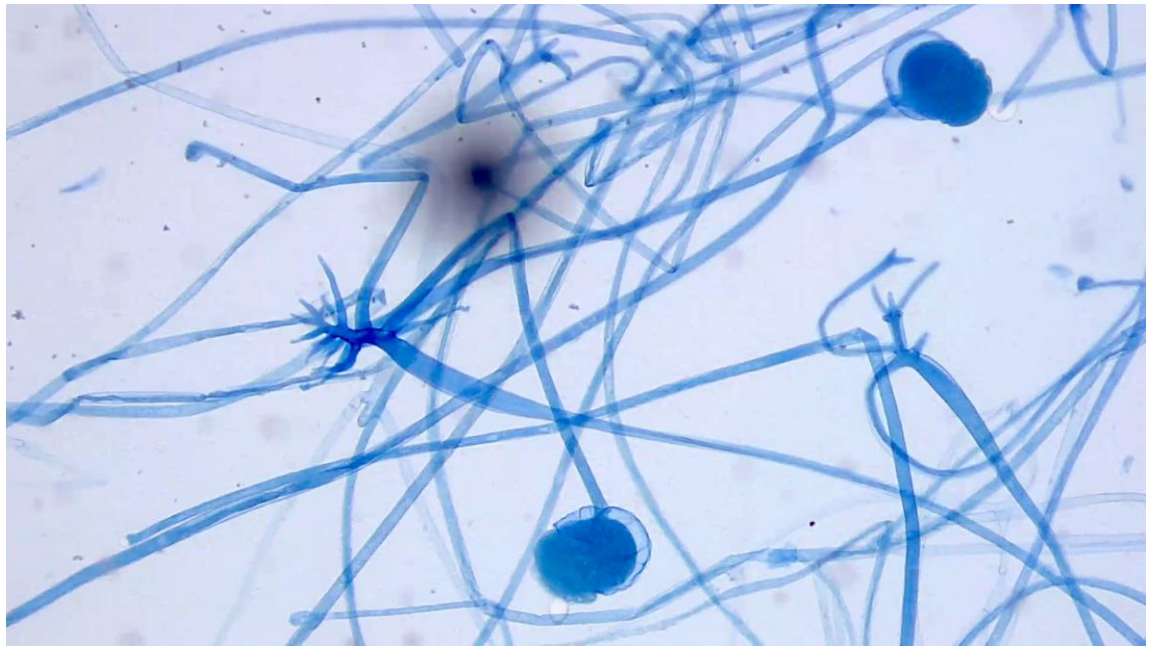
Tanı

- Erken tanı prognozda çok etkili
- Risk faktörlerinin değerlendirilmesi + Klinik + Görüntüleme
- Histopatoloji, Kültür, Moleküler Yöntemler

- **Kantitatif multiplex PCR**: Mucor/Rhizopus, Lichtheimia and Rhizomucor 18S rRNA hedefli, erken dönemde kandan DNA izolasyonu.

Tanı

- Küfler çok frajil yapıda, doku ezilmemeli
- Direk bakı: geniş açılı septasız hif
- 25-37 C ‘de üreme
- Steril alanlardan kültür
- Kan kültürü genellikle negatif



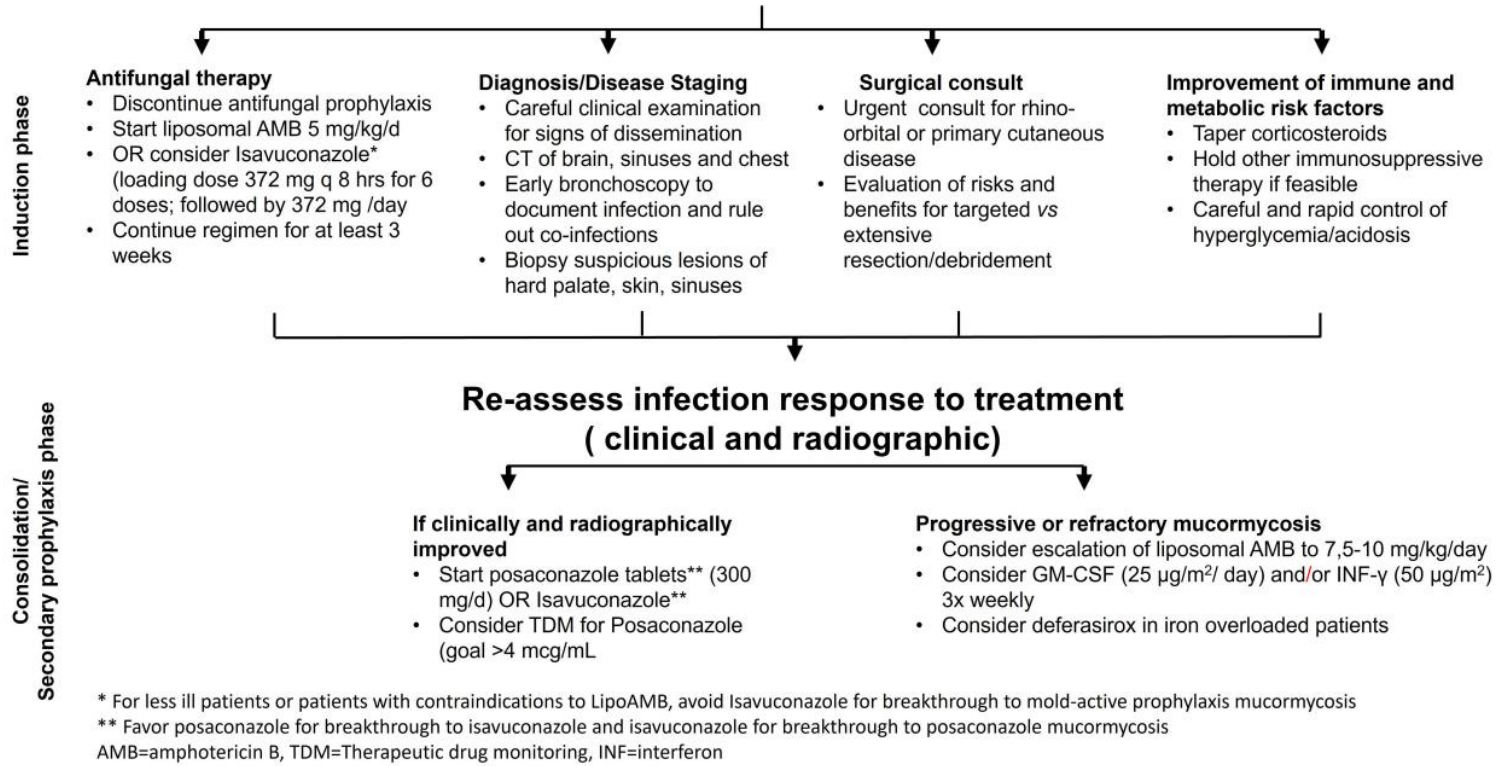


FIGURE 4
An Algorithm for Mucormycosis Treatment.

Görüntüleme

- Tanı ve takipte
- BT (sinüs ve akciğer, batın)
- MR (orbital, santral sinir sistemi)

Görüntüleme

- Akciğer: Çoğunlukla aspergillus (Hematolojik maligniteli hastalarda mucor'un en sık tutulduğu alan)
  - Ters halo: Çoğunlukla mucor (Fakat, tuberküloz, aspergillus…..)
  - >10 nodüler infiltrat
  - >3 cm nodül
  - Plevral efüzyon
  - Halo: Çoğunlukla aspergillus (Mucor, tuberculosis, CMV, nocardia……)
- Rhino-orbita-cerebral : Hematolojik maligniteli hastada çoğunlukla mucor (Fakat, aspergillus….)
  - Kemik yıkımı
  - Mukozal kalınlaşma
  - İntrakranial yayılım

Evrelendirme

- Tutulum yeri, semptom, bulgu ve tanıya göre
- Nazal/Paranazal/ Orbita/ SSS tutulumu
- 4 evre

Proposed Staging of Rhino-Orbito-Cerebral Mucormycosis (ROCM)

Staging of Rhino-Orbito-Cerebral Mucormycosis	Symptoms	Signs	Primary Assessment	Confirmation of Diagnosis
Stage 1: Involvement of the nasal mucosa 1a: Limited to the middle turbinate 1b: Involvement of the inferior turbinate or ostium of the nasolacrimal duct 1c: Involvement of the nasal septum 1d: Bilateral nasal mucosal involvement	Nasal stuffiness, nasal discharge, foul smell, epistaxis	Foul-smelling sticky mucoid or black-tinged, or granular or haemorrhagic nasal discharge, nasal mucosal inflammation, erythema, violaceous or blue discoloration, pale ulcer, anaesthesia, ischemia, eschar	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Deep nasal swab or endoscopy-guided nasal swab or nasal mucosal biopsy for direct microscopy, culture and molecular diagnostics; nasal mucosal biopsy for rapid histopathology with special stains
Stage 2: Involvement of paranasal sinuses 2a: One sinus 2b: Two ipsilateral sinuses 2c: > Two ipsilateral sinuses and/or palate/oral cavity 2d: Bilateral paranasal sinus involvement or involvement of the zygoma or mandible	Symptoms in Stage 1 + facial pain, facial edema, dental pain, systemic symptoms (malaise, fever)	Signs in Stage 1 + unilateral or bilateral, localized or diffuse facial edema, edema localized over the sinuses, localized sinus tenderness	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 1 + sinus biopsy for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 3: Involvement of the orbit 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected 3c: Central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis; involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement	Symptoms in Stage 1 and 2 + pain in the eye, proptosis, ptosis, diplopia, loss of vision, infraorbital and facial V1 V2 nerve anesthesia	Signs in Stage 1 and 2 + conjunctival chemoses, isolated ocular motility restriction, ptosis, proptosis, infraorbital nerve anesthesia, central retinal artery occlusion, features of ophthalmic artery occlusion and superior ophthalmic vein thrombosis. V1 and V2 nerve anesthesia, and features of III, IV and VI nerve palsy indicating orbital apex/superior orbital fissure involvement.	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 2 + orbital biopsy if indicated and if feasible (if the disease is predominantly orbital) for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 4: Involvement of the CNS 4a: Focal or partial cavernous sinus involvement and/or involvement of the cribriform plate 4b: Diffuse cavernous sinus involvement and/or cavernous sinus thrombosis 4c: Involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction 4d: Multifocal or diffuse CNS disease	Symptoms in Stage 1 to 3 + bilateral proptosis, paralysis, altered consciousness, focal seizures	Signs in Stage 1-3 (some features overlap with Stage 3) + V1 and V2 nerve anesthesia, ptosis, and features of III, IV and VI nerve palsy indicate cavernous sinus involvement. Bilaterality of these signs with contralateral orbital edema with no clinico-radiological evidence of paranasal sinus or orbital involvement on the contralateral side indicate cavernous sinus thrombosis. Hemiparesis, altered consciousness and focal seizures indicate brain invasion and infarction.	Diagnostic endoscopy, Contrast-enhanced CT Scan, MRI (preferred)	Same as Stage 3

Figure 1: Proposed staging of Rhino-Orbito-Cerebral Mucormycosis with clinical symptoms and signs, evaluation and diagnosis

Tedavi

- Altta yatan hastalığın tedavisi
- Uygun ve erken cerrahi debridman
- Antifungal tedavi

Tedavi

- Amfoterisin B
- Posakonazol
- Isavukonazol

- Azol duyarlılığı türe göre değişebilmekte
  - *Mucor*- posakonazol yüksek MİK
  - *Rhizomucor*- isavukonazol yüksek MİK
  - MDR: *Cunninghamella* ve bazı *Rhizopus* spp

Almyroudis et al., 2007; Lamoth and Kontoyiannis, 2019; Borman et al., 2021

Management Approach for Possible, Probable or Proven Rhino-Orbito-Cerebral Mucormycosis (ROCM)

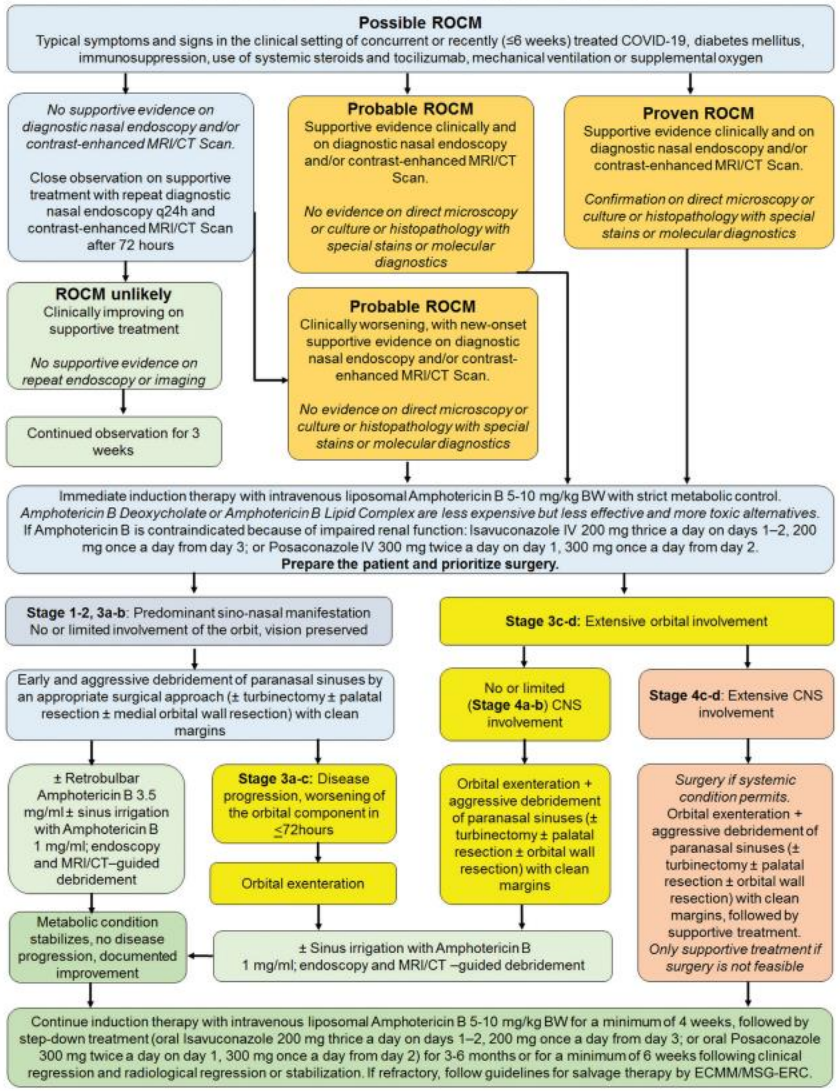


Figure 2: Management algorithm for Rhino-Orbito-Cerebral Mucormycosis (ROCM)

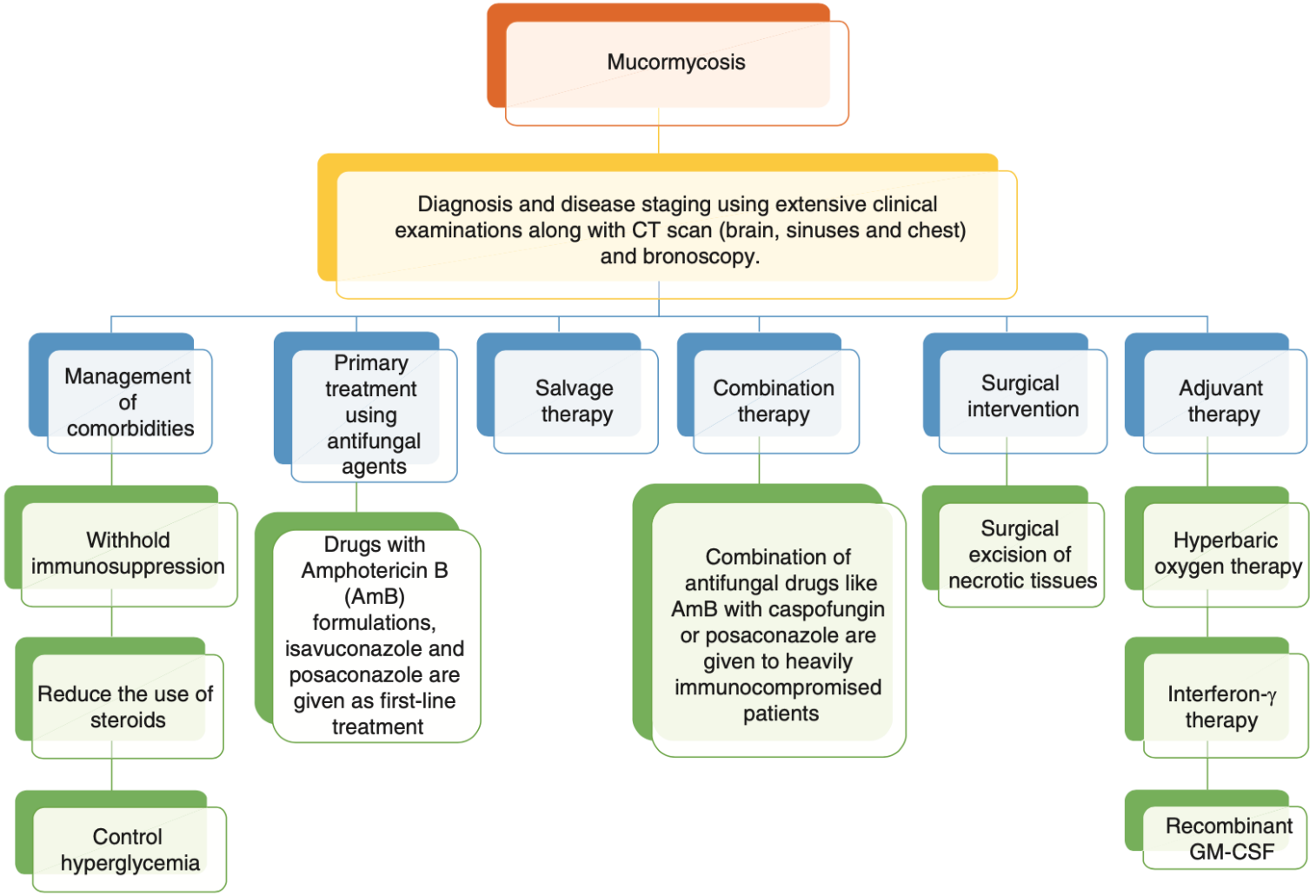
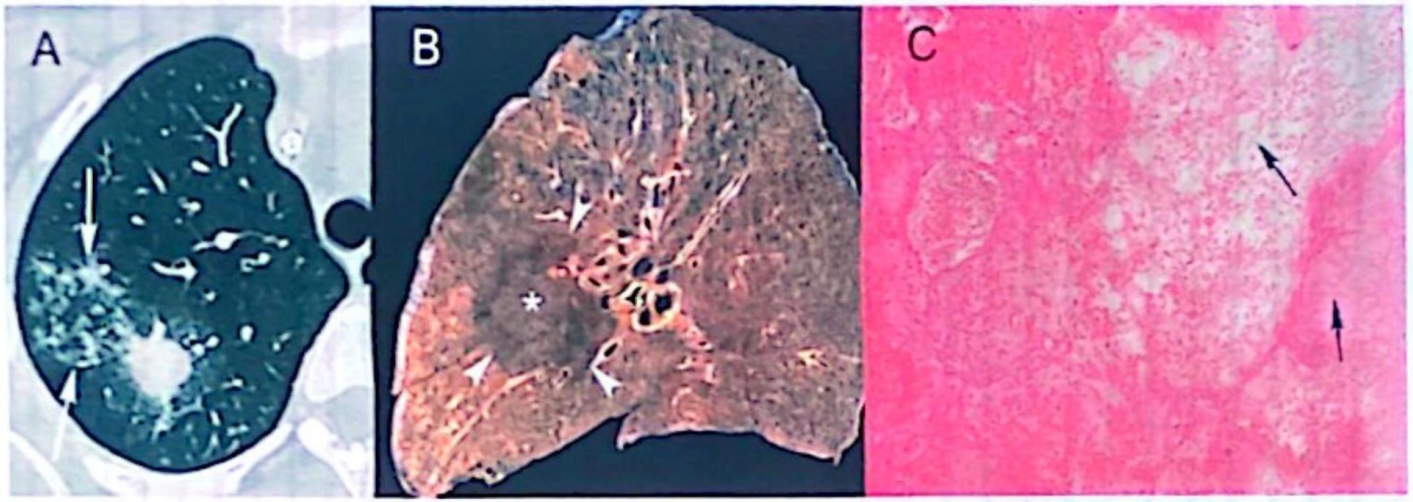


Figure 6. Treatment strategies for mucormycosis.
GM-CSF: Granulocyte macrophage colony-stimulating factor.

Are we delivering antifungals to the site of infection?



- Established fungal lesions are characterized by extensive tissue necrosis

Yüksek doz?

Is high-dose liposomal AMB for mucormycosis?

- AMBIZYGO study: I-II prospective open label study by the French MSG
- LipoAMB 10mg/kg/d, median duration was (only) 14 days
- 40 pts, 53% with hematologic cancer
- Sites: Lungs 29%, rhino-orbital in 26%, dissemination in 18%, skin 18%
- *Leicheimia* spp the most common Mucorales
- Some surgery in 71%, in 9/9 of pts wjth rhino-orbital MCR
- Poor tolerability: 40% required reduction of lipoAMB dose (to 7,5mg/kg/d) due rising creatinine
- Modest responses: 38% wk 4, 45% wk 12
- Overall mortality: 38% wk 12, 53% wk 24

Destek tedavi seçenekleri

- Hiperbarik oksijen tedavisi
- GCSF
- Topikal antifungal tedavi
- Konvansiyonel antifungal kullanım
  - Aerosol, irrigan, direk enjeksiyon, antifungal emdirilmiş sement

Drew RH, Perfect JR. Fungi 2022

Vuong N,. Jfungii 2023

Hyperbaric Oxygen Therapy (HBOT): Logistically difficult, expensive

- The patient breaths directly pressurized 100% O2
- Patients are monitored remotely
- "Air breaks" that are times when patients received room air are usually given once or twice during the session

Özetle

- Fırsatçı, anjioinvaziv
- Predispozan faktörler: Diyabeti nötropeni, uzun süreli kortikosteroid, organ transplantasyonu
- Etken: Mucorales takımının 38 türü
  - *Mucor* spp, *Rhizopus* spp., *Lichthemia* spp
- Fungal sporlarla-İnhalasyon veya hasarlı deriden
- Tedavi: Yüksek doz L-AmB, isavukonazol ve uygun cerrahi girişim, altta yatan faktörün kontrolü

TEŞEKKÜR EDERİM