Mukormikoz

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

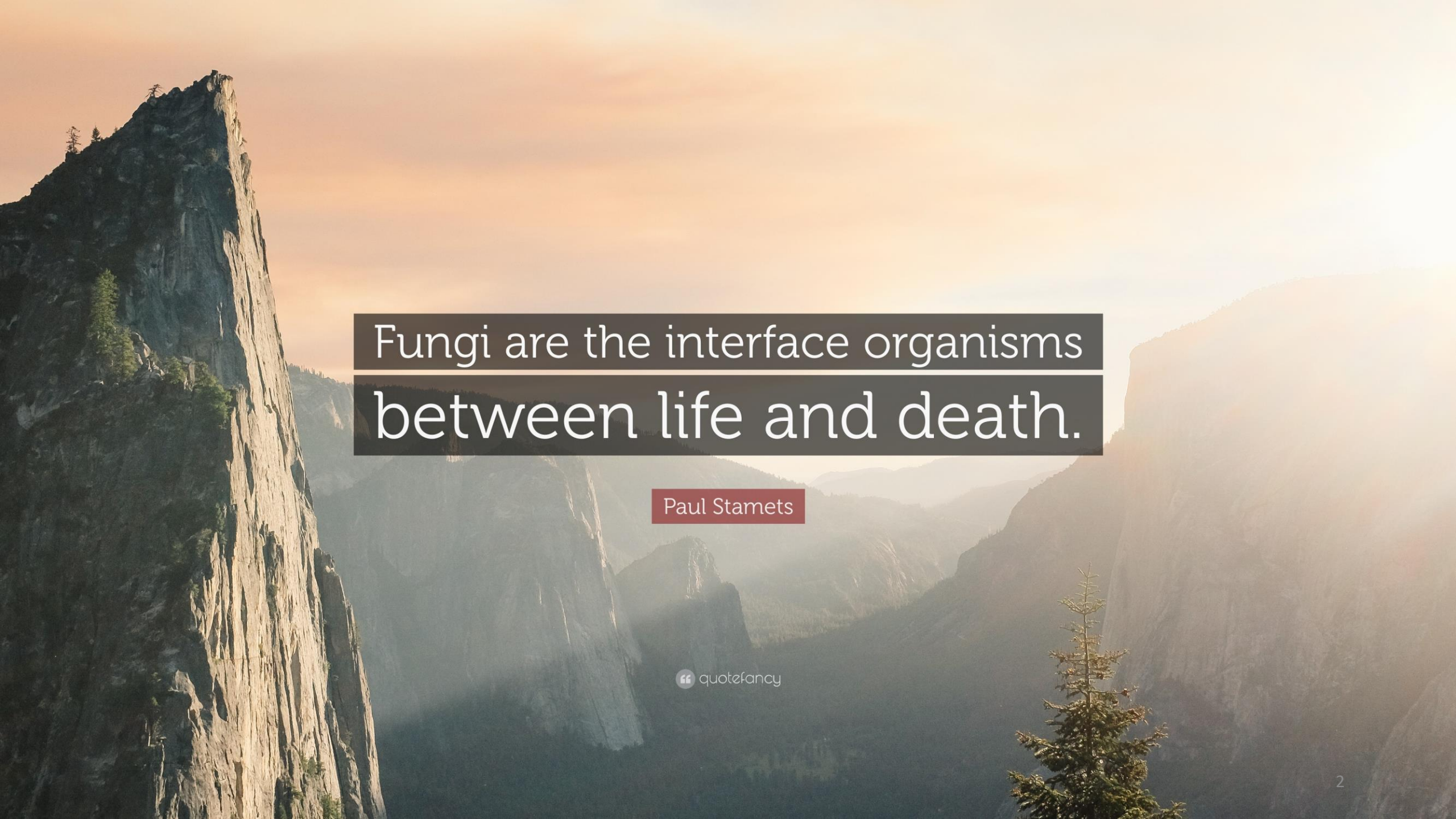
Oturum Başkanları: **Yasemin Çağ, Canan Ağalar**

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**

Dr. Süheyla Kömür

ÇÜTF ENFEKSİYON HASTALIKLARI AD

12. TÜRKİYE EKMUD BİLİMSEL KONGRESİ


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

FUNGAL BIOLOGY REVIEWS 31 (2017) 12–32

ELSEVIER

British Mycological Society promoting fungal science

journal homepage: www.elsevier.com/locate/fbr

Review

Mucor: A Janus-faced fungal genus with human health impact and industrial applications

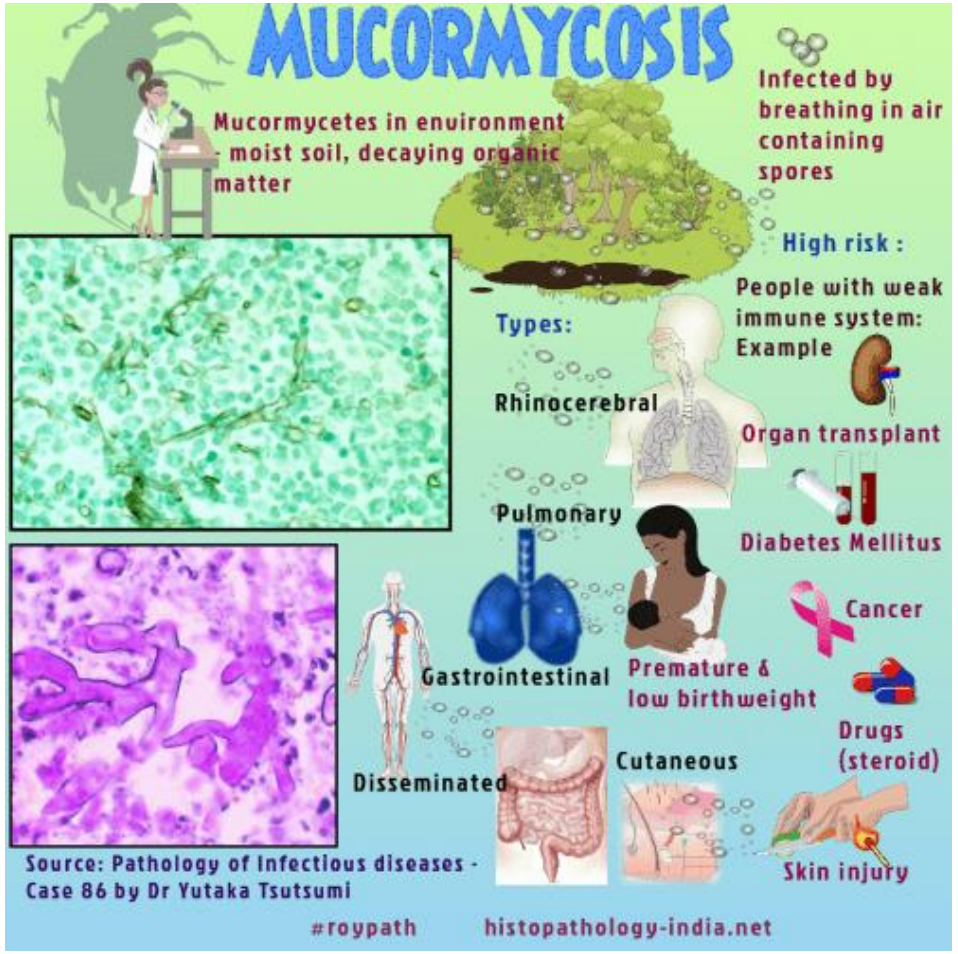
*Stéphanie MORIN-SARDIN, Patrice NODET, Emmanuel COTON, Jean-Luc JANY**

Université de Brest, EA 3882 Laboratoire Universitaire de Biodiversité et d'Ecologie Microbienne, IBSAM, ESIAB, Technopôle Brest-Iroise, 29280 Plouzané, France

Biyoteknolojide yaygın kullanım

- Geniş sıcaklık aralığında hızlı üreme
- Termofilik kapasite
- Proteolitik ve lipolitik enzim aktivitesi

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

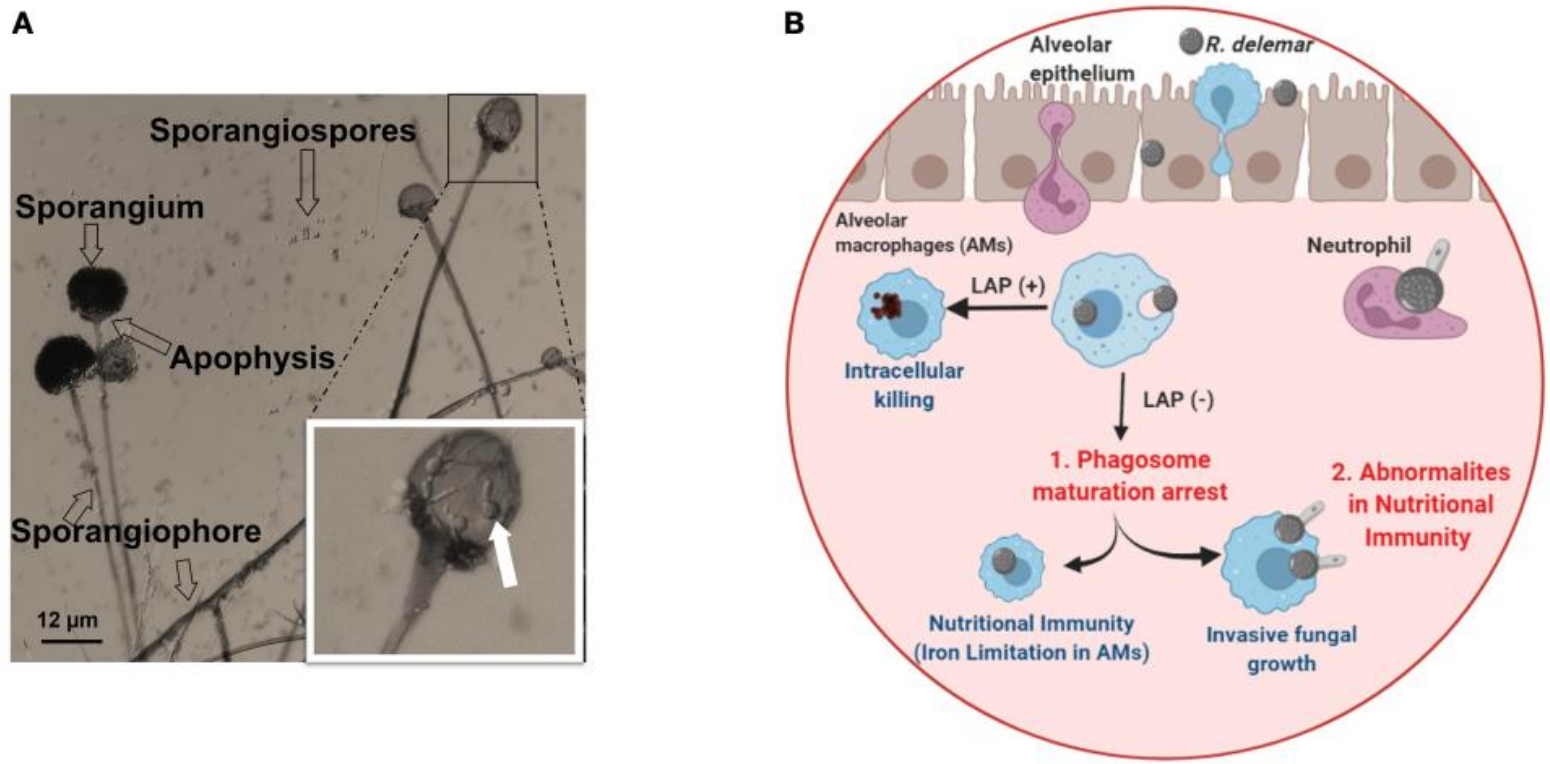


FIGURE 2
(A) Morphology of *Rhizopus delemar*. Sporangia form at the apices of sporangiophores and contain the asexual sporangiospores. Germinated spores seen in the sporangium magnified box can be an overlay of the sporangium on released and germinated spores. **(B)** Under normal circumstance, alveolar 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".

- **Sporların inhalasyonu**
  - Rhino-orbital/serebral
  - Sino-pulmoner
- **Travma -** ciltten geçiş
  - Kutanöz

Nazal ve alveoler epitel hücre invazyonu: Glucose-regulated protein 78kDa (GRP78) Epidermal büyüme faktörü aktivasyonu kaskatı

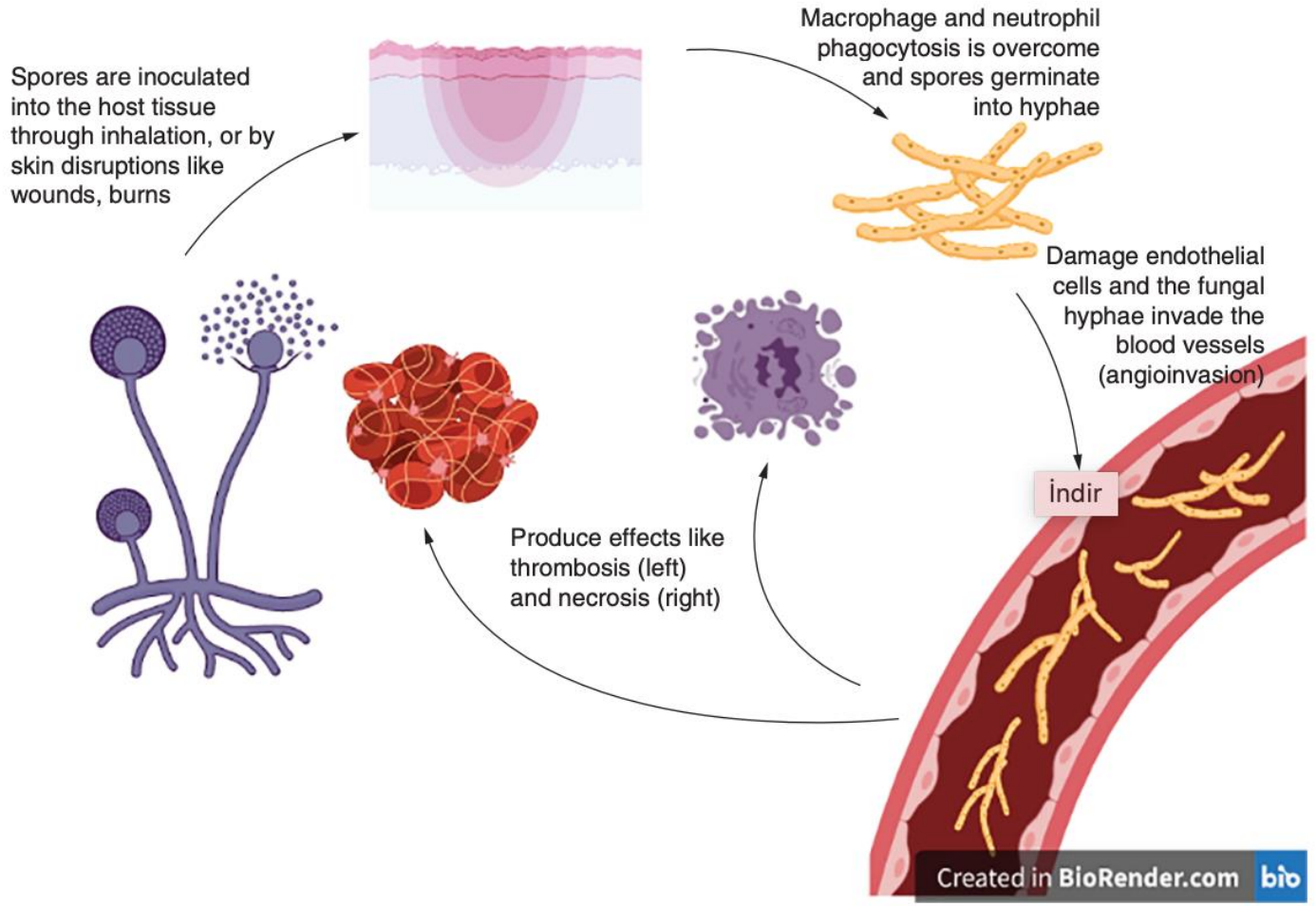
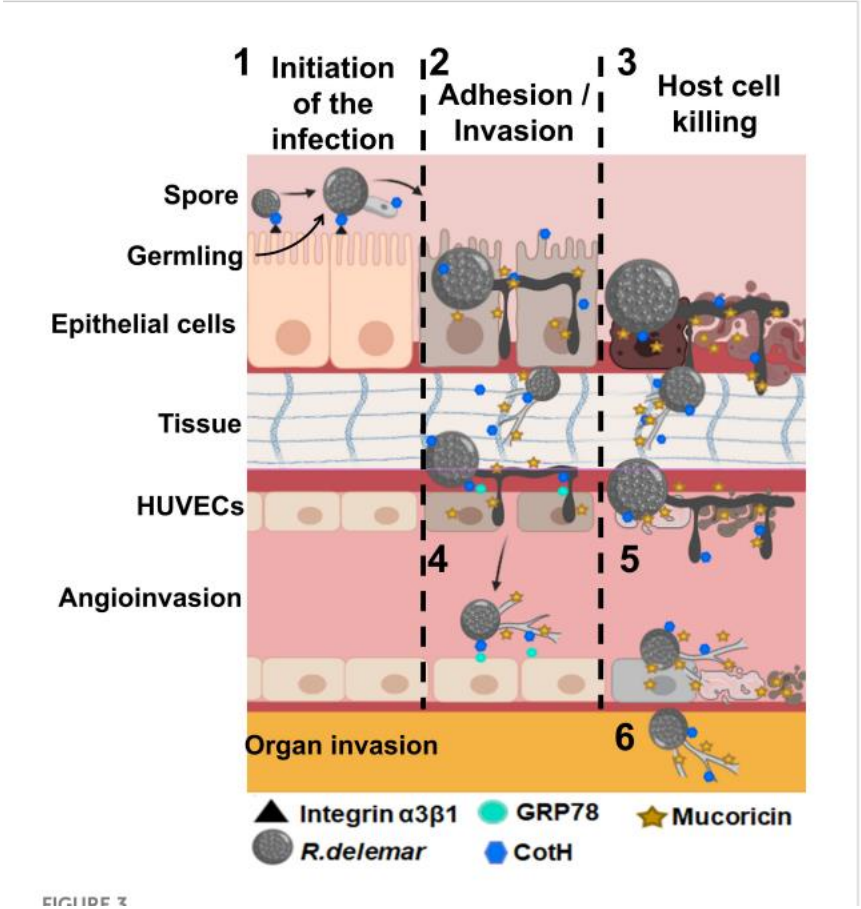


Figure 3. General mechanism of pathogenesis in mucormycosis.
Created with BioRender.com, reference no. 2945-5180.

Alqarihi A, et al. Front. Cell. Microbiol. 2023

Patojenite faktörleri

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



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**

Frac et al, 2018
Andrianaki et al., 2018

Epidemiyoloji

- Son 15 yılda artışta, mortalite >%50
- Pek çok ülkeden bildirimler mevcut
- Hindistan- COVID-19 pandemisi ile hiperendemik
- 3. sıklıkta invaziv mantar enfeksiyon etkeni
- Transplant ünitelerinde artış
  - Vorikonazol profilaksisi suçlanmakta

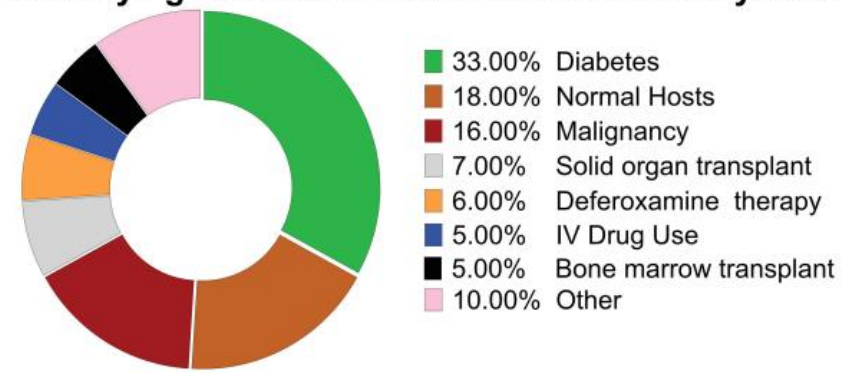
Gupta et al., 2023
Roden et al., 2005
Ambrosioni et al., 2010
Kontoyiannis et al., 2000
Petrikkos et al., 2012

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

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

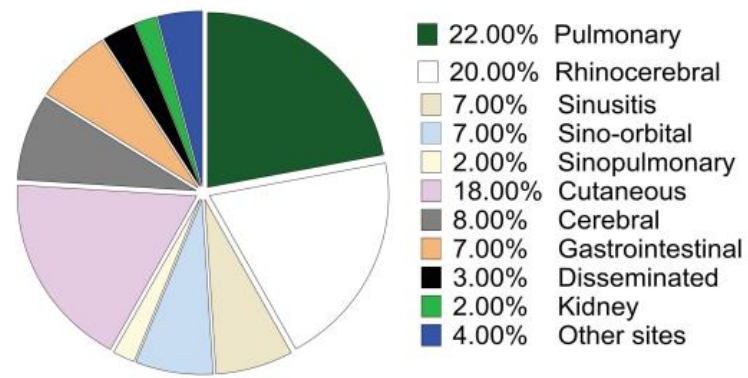
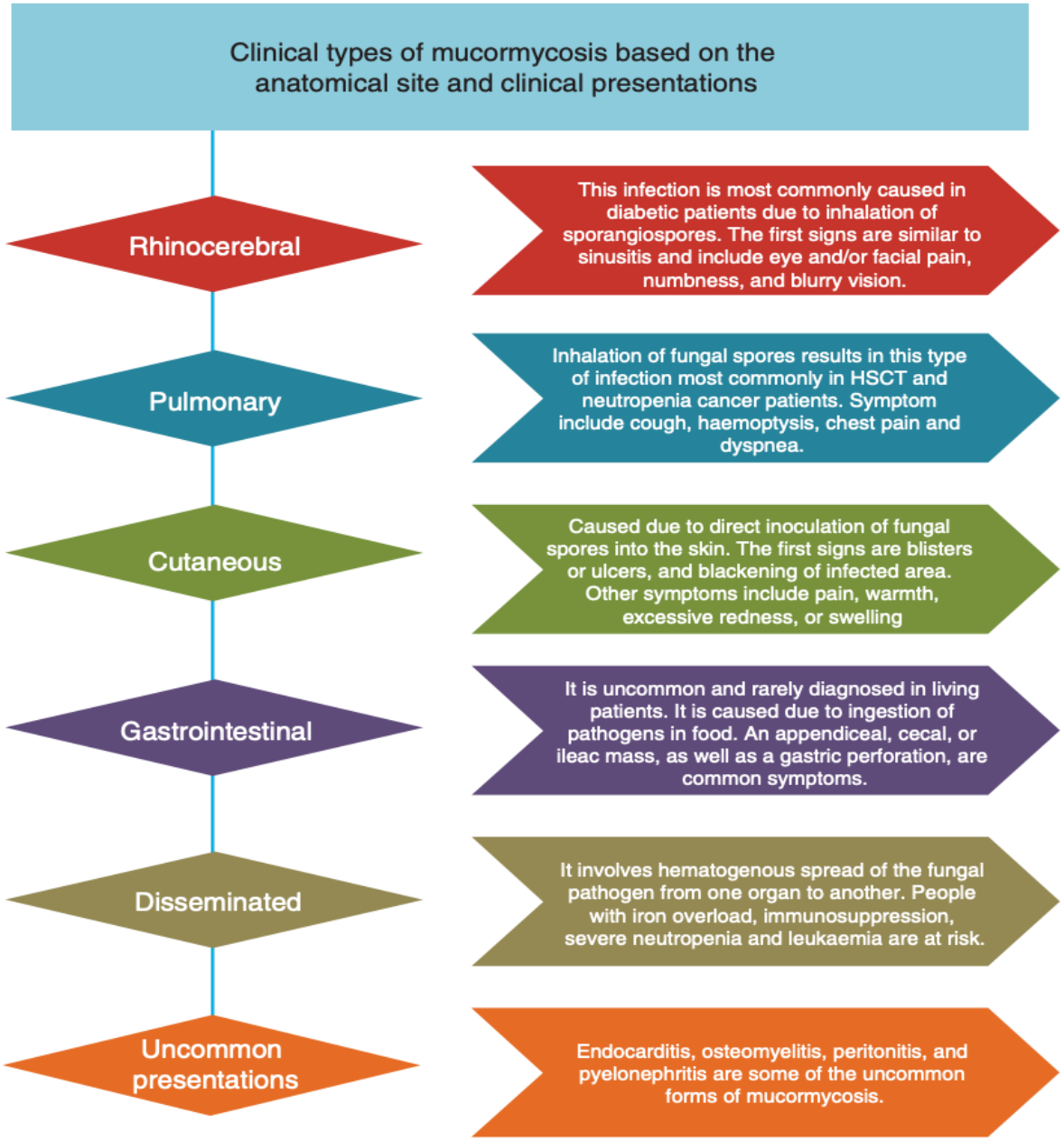


FIGURE 1
Frequency of mucormycosis manifestation in susceptible hosts and the etiologic agents of the disease. **(A)** Frequency of mucormycosis by underlaying predisposing host condition. **(B)** Etiological agents of mucormycosis. **(C)** Frequency of different types of mucormycosis reported.
* Data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

Klinik Tutulum

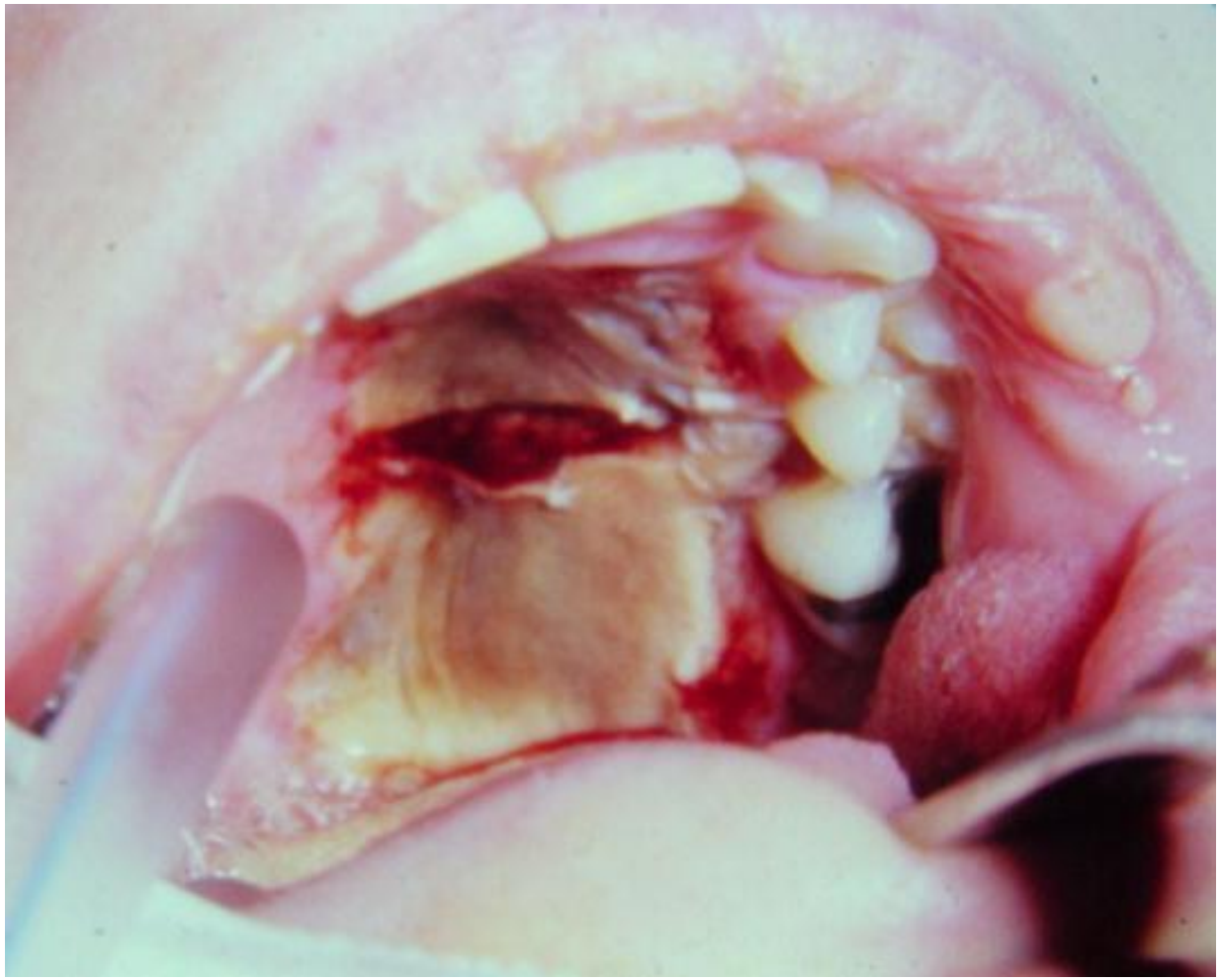


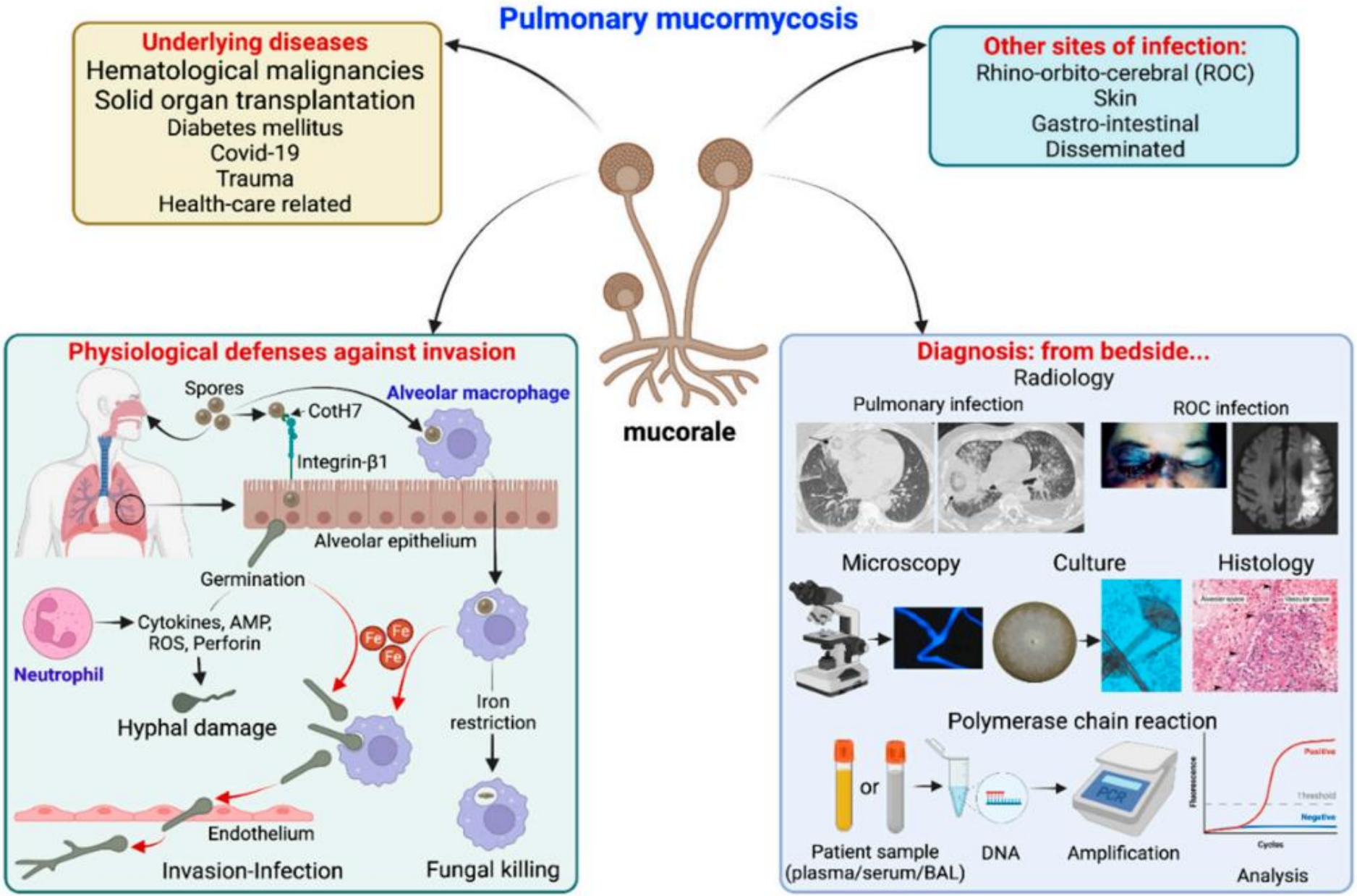
Future Microbiol. (2023) 18(3)

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

Rino-orbito-serebral mukormikozdan şüphelen!

- Nazal dolgunluk
- Kötü koku
- Epistaksis
- Nazal akıntı
- Nazal mukozda eritem, mor-siyah renk değişikliği, ülser
- Göz kapağı, perioküler veya fasiyal ödem/renk değişikliği
- Orbita, paranazal sinüs, dental lokal ağrı
- Fasiyal ağrı/paralizi
- Başağrısı
- Propitoz
- Ani görme kaybı
- Oküler hareket kısıtlılığı
- Ateş, bilinç değişikliği, fokal nöbet




Pulmonary mucormycosis
Underlying diseases
Hematological malignancies
Solid organ transplantation
Diabetes mellitus
Covid-19
Trauma
Health-care related
Other sites of infection:
Rhino-orbito-cerebral (ROC)
Skin
Gastro-intestinal
Disseminated
mucorale
Physiological defenses against invasion
Spores
CotH7
Alveolar macrophage
Integrin-β1
Alveolar epithelium
Germination
Neutrophil
Cytokines, AMP, ROS, Perforin
Fe
Hyphal damage
Iron restriction
Endothelium
Invasion-Infection
Fungal killing
Diagnosis: from bedside...
Radiology
Pulmonary infection
ROC infection
Microscopy
Culture
Histology
Polymerase chain reaction
or
PCR
Patient sample (plasma/serum/BAL)
DNA
Amplification
Analysis

Pulmoner Mukormikoz

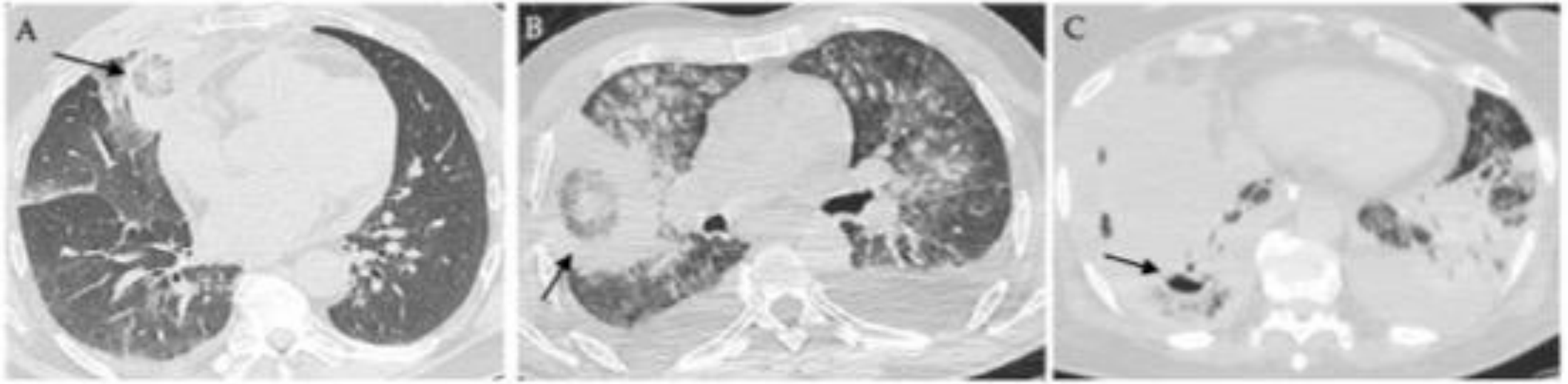


Figure 2. Images of pulmonary mucormycosis. (**A**) Reversed halo sign (indicated with an arrow) in a patient with hematological malignancy; (**B**) Reversed halo sign HS (arrow) in a patient with COVID-19; (**C**) Cavitation (arrow) in a condensation in a patient with COVID-19 and lung tumor.

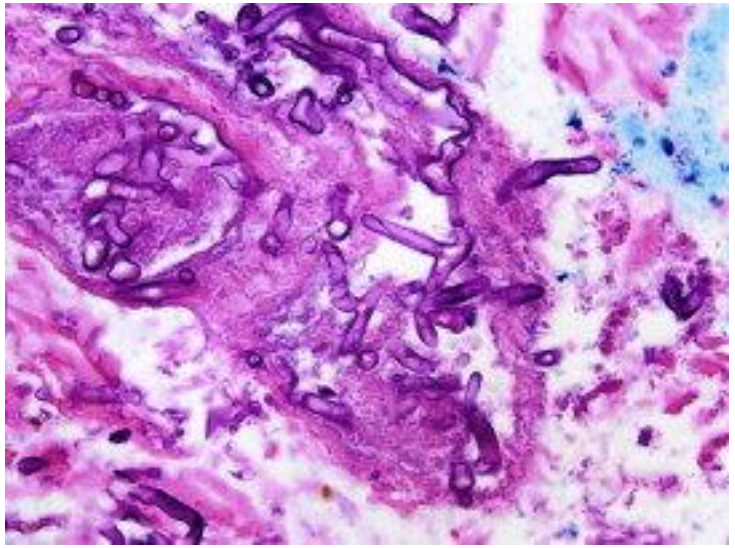
- Hematolojik kanserlerde en sık görülen form
- Koenfeksiyon şeklinde olabilir (+aspergilloz/tbc/COVID-19 vs)
- Breakthrough mantar enfeksiyonu olarak

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

Tanıda Direk mikroskobik inceleme

- Geniş, septasız, geniş açılı veya dik açılanma gösteren kalın duvarlı şerit benzeri hifler
- KOH
- Gomori metenamin gümüş boyama
- Hematoksilen eozin
- PAS



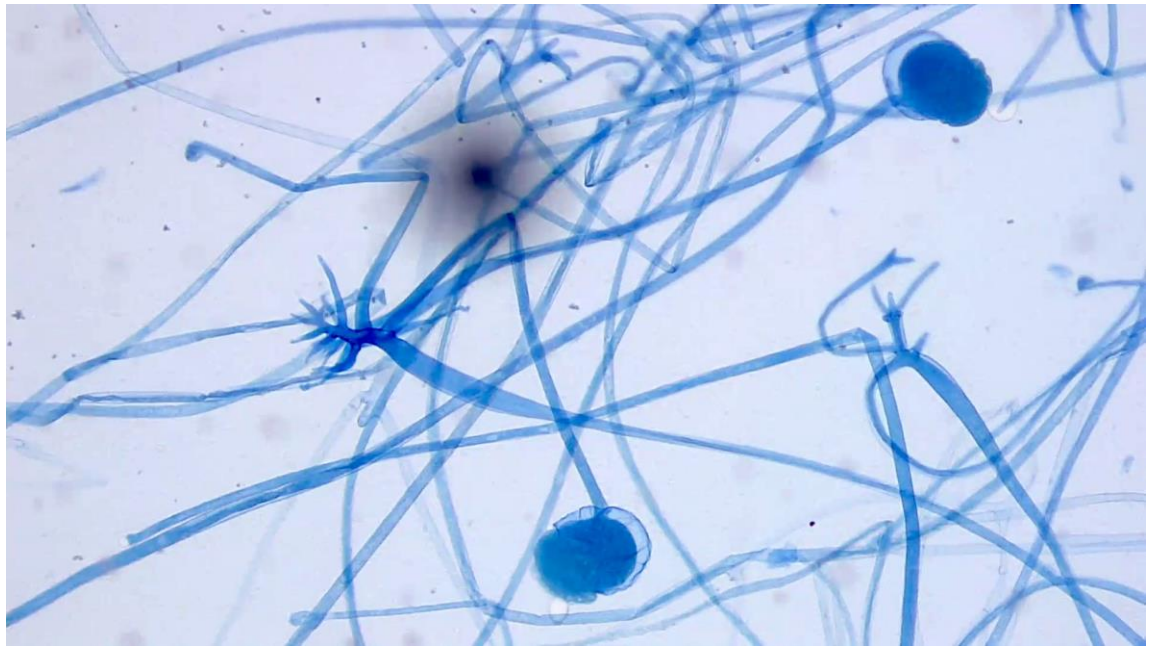
Tanı

- 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

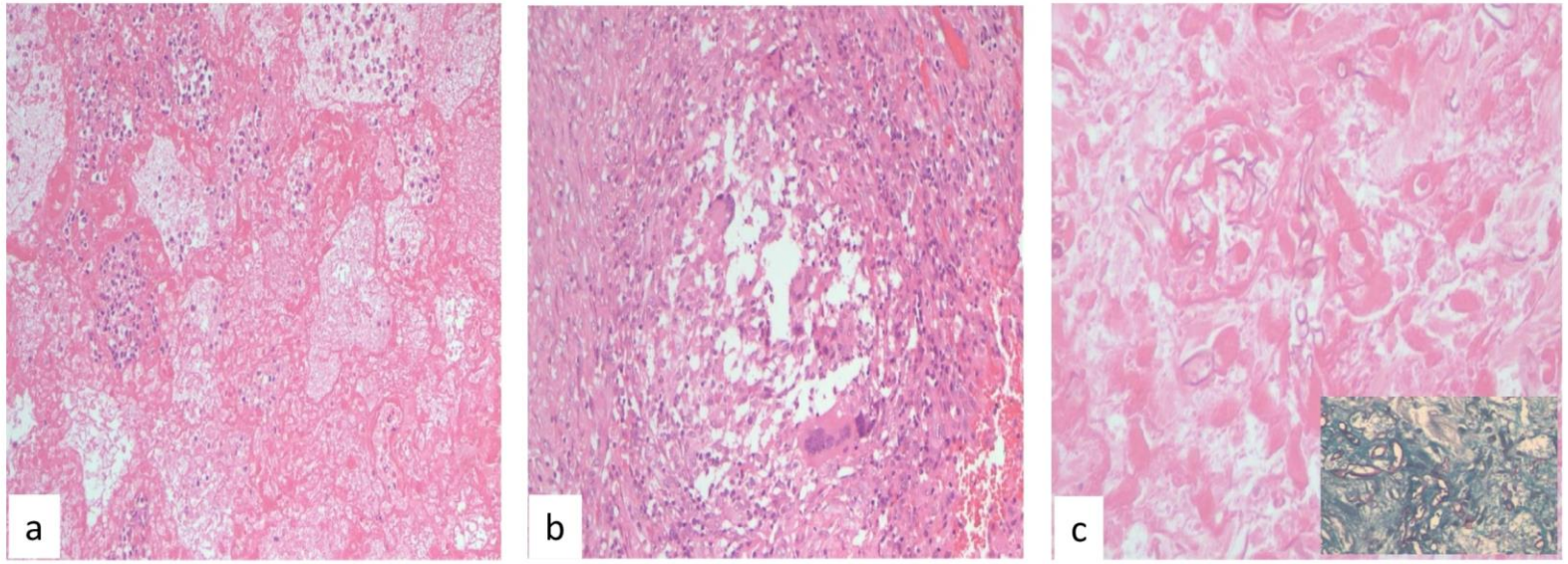
- Küfler çok frajil yapıda, doku ezilmemeli
- 25-37 C ‘de üreme
- Steril alanlardan kültür
- Kan kültürü genellikle negatif



Histopatoloji

1.Vasküler invazyon

2.Iskemik veya hemorajik nekroz



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

Mukorimikoz Tedavi Yönetimi

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

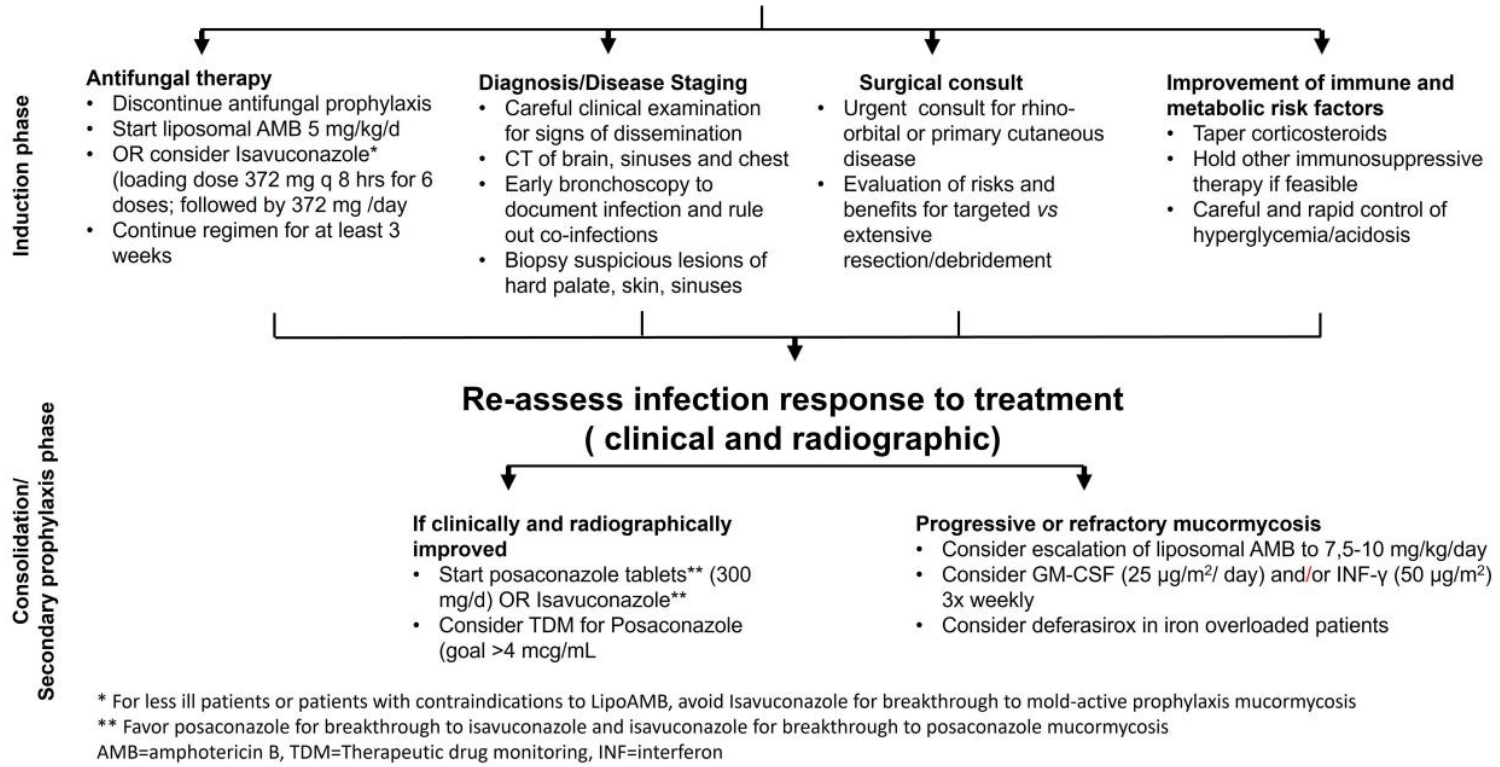


FIGURE 4
An Algorithm for Mucormycosis Treatment.

Algarihi et al, 2023

Evrelendirme

- Tutulum yeri, semptom, bulgulara 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

- 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

Diyabet
İmmünsupresyon
Steroid kullanımı
Tosilizumab
Mekanik ventilasyon
+COVID-19

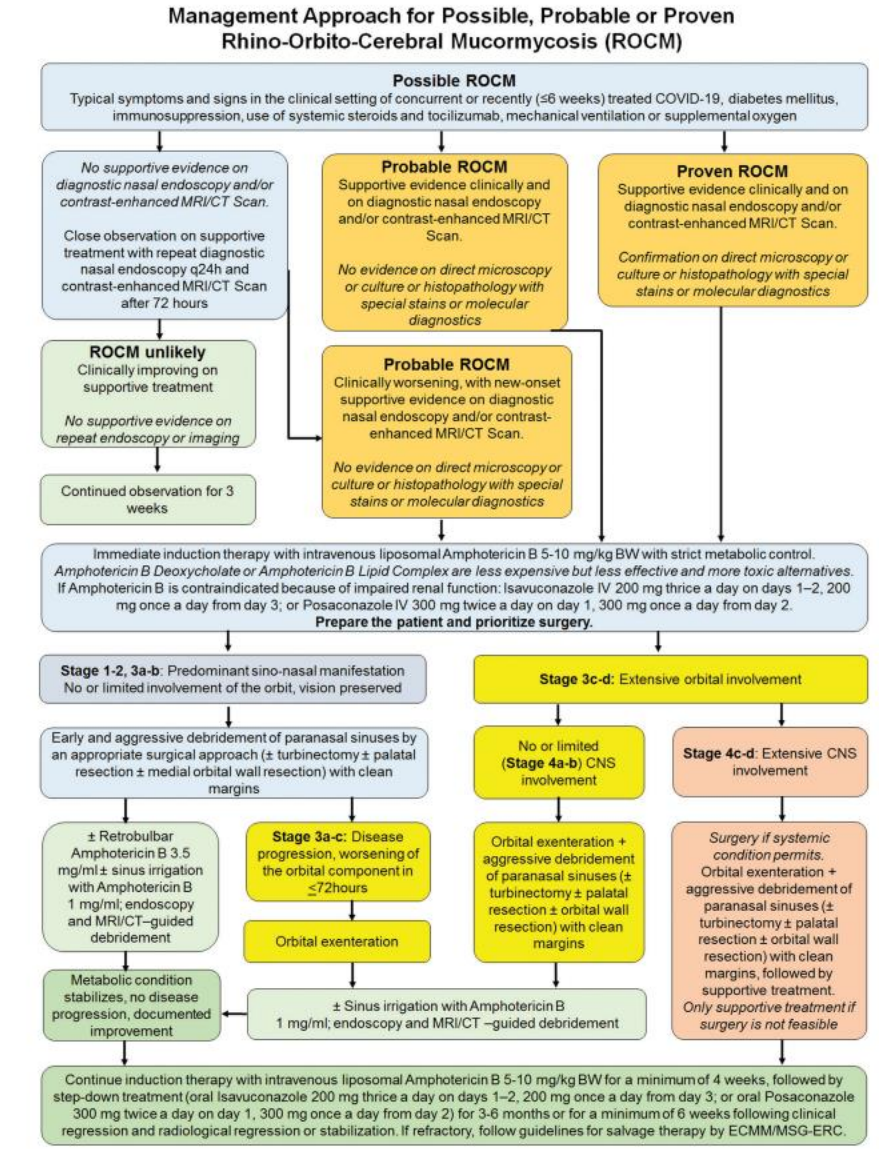


Figure 2: Management algorithm for Rhino-Orbito-Cerebral Mucormycosis (ROCM)

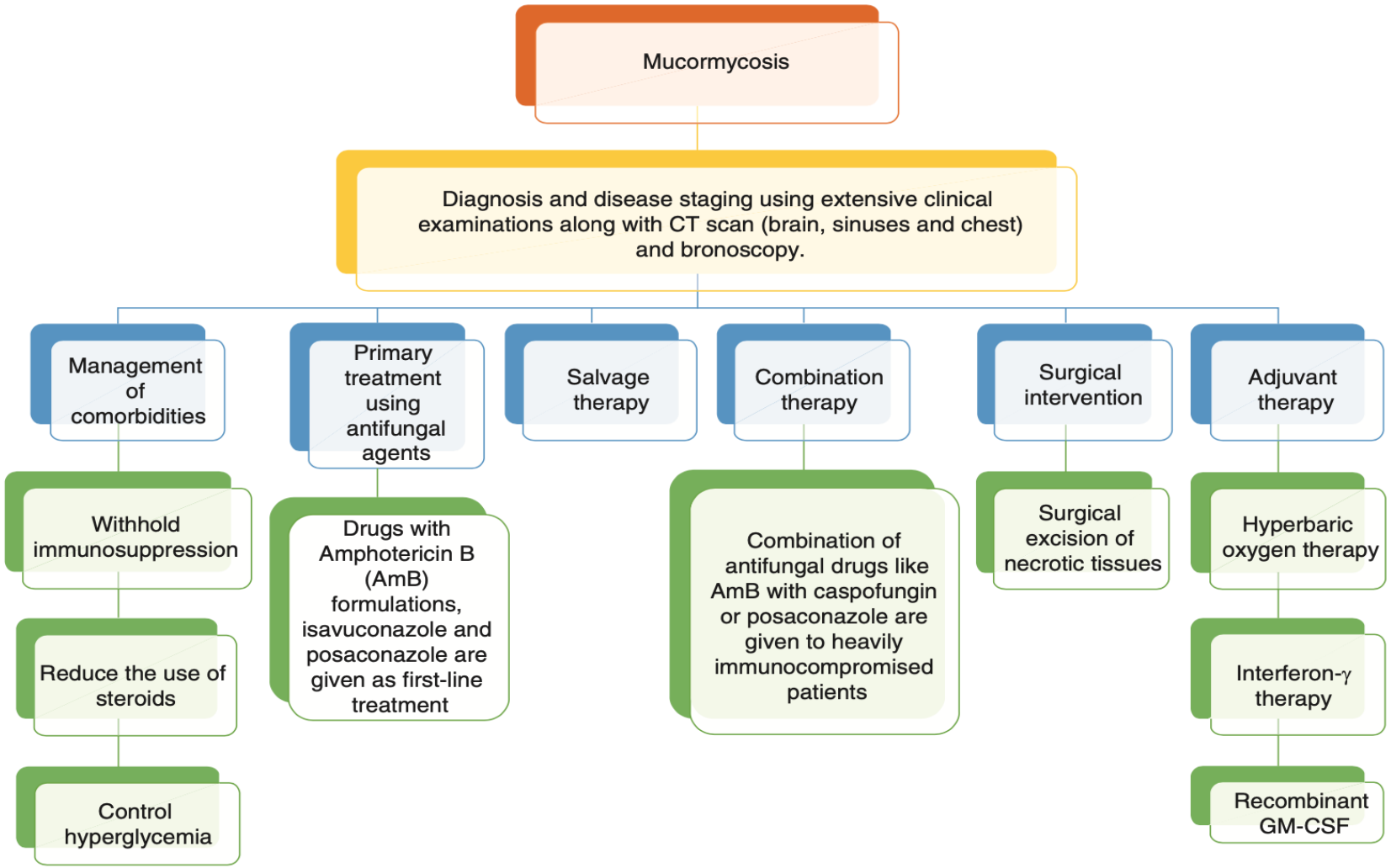


Figure 6. Treatment strategies for mucormycosis.
GM-CSF: Granulocyte macrophage colony-stimulating factor.

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2019, 57, S161–S167
doi: 10.1093/mmy/myy067
Review Article

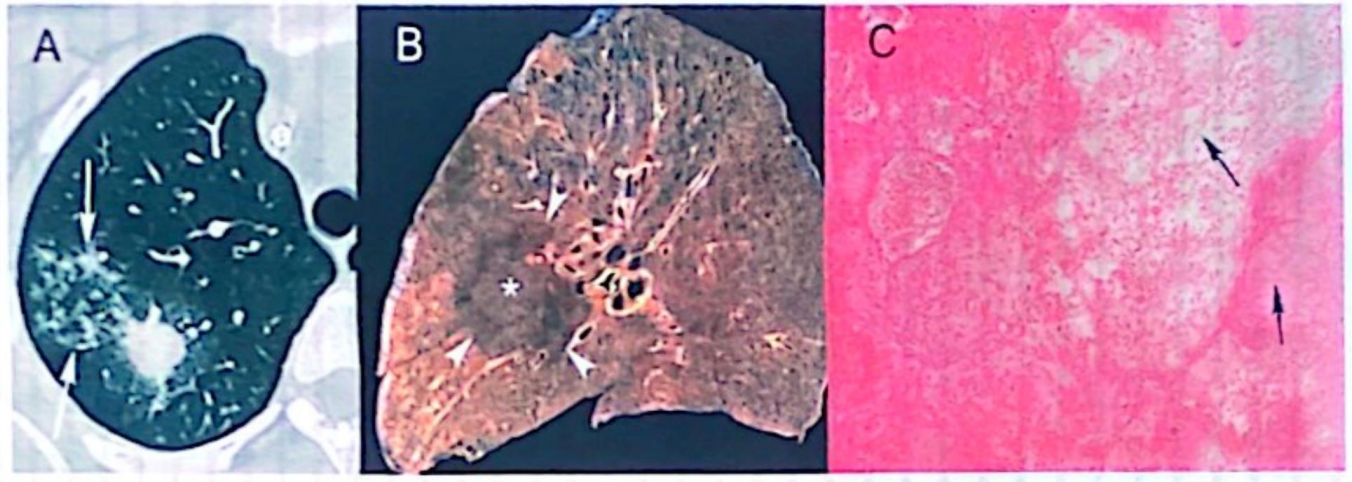
Review Article

Beyond tissue concentrations: antifungal penetration at the site of infection

Yanan Zhao[1,*], Brendan Prideaux[1], Shane Baistrocchi[2], Donald C. Sheppard[2] and David S. Perlin[1]

[1]Public Health Research Institute, New Jersey Medical School, Rutgers Biomedical and Health Sciences, Newark

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

Combination Therapy for Mucormycosis: Why, What, and How?

Brad Spellberg,[1,2] Ashraf Ibrahim,[2,3] Emmanuel Roilides,[7] Russel E. Lewis,[4,5] Olivier Lortholary,[9,10] George Petrikkos,[8] Dimitrios P. Kontoyiannis,[5] and Thomas J. Walsh[6]

Table 1. Options for Combination-Therapy Studies for Mucormycosis

Combination Therapy With Lipid Polyene	Pros	Cons
Echinocandins	Very safe; intravenous formulations available; strong preclinical data; concordant observational clinical study	Will industrial sponsor pay for study?
Deferasirox	Strong preclinical data; concordant observational clinical data (highly limited)	Phase II DEFEAT Mucor study failed to show benefit, and there was excess mortality in patients who received deferasirox therapy, particularly in those with active hematological malignancy; no intravenous formulation; will industrial sponsor pay for study?
Posaconazole	Safe; in vitro activity against some Mucorales	Preclinical data poor; no clinical data; pharmacokinetic-pharmacodynamic concerns; no intravenous formulation; will industrial sponsor pay for study?
Isavuconazole	In vitro activity against Mucorales; intravenous formulation in late-stage development	No combination-therapy data in mice and no clinical data yet available; will industrial sponsor pay for study?
Echinocandins plus deferasirox	Maximal aggressiveness	Study would be large to enable comparison with both dual-therapy options; safety concerns and no intravenous formulation for deferasirox

Abbreviation: DEFEAT Mucor, Deferasirox–AmBisome Therapy for Mucormycosis.

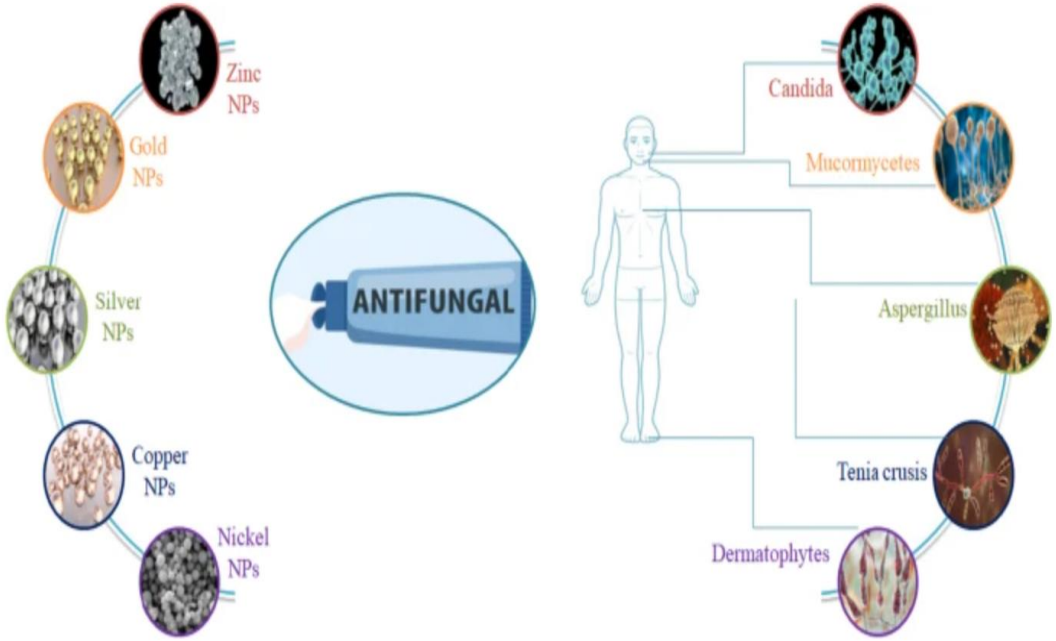
Journal of *Fungi*

MDPI

Review

Conventional Antifungals for Invasive Infections Delivered by Unconventional Methods; Aerosols, Irrigants, Directed Injections and Impregnated Cement

Richard H. Drew [1,2,*] and John R. Perfect [1]



Nanoparticles assisted intra and transdermic delivery of antifungal ointment: an updated review

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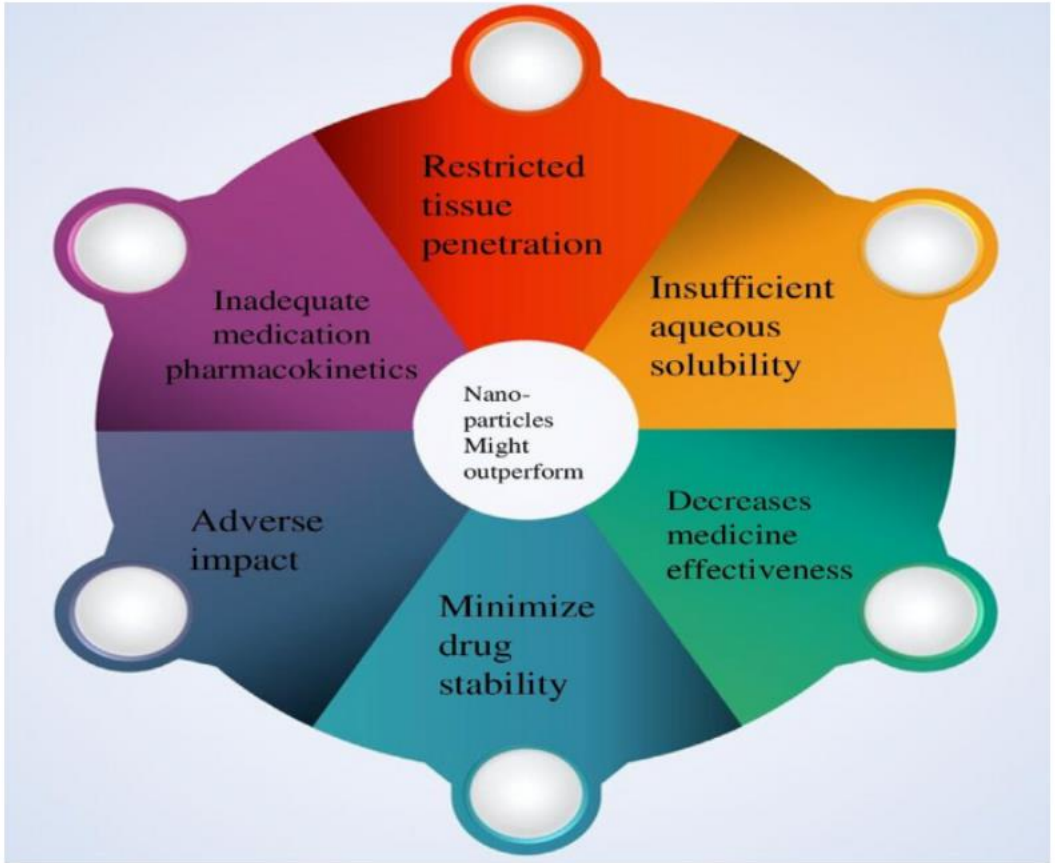

Destek tedavi seçenekleri

- 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
- Hasta bazında değerlendirme
- Erken tanı önemli
- Multidisipliner yaklaşım

TEŞEKKÜR EDERİM