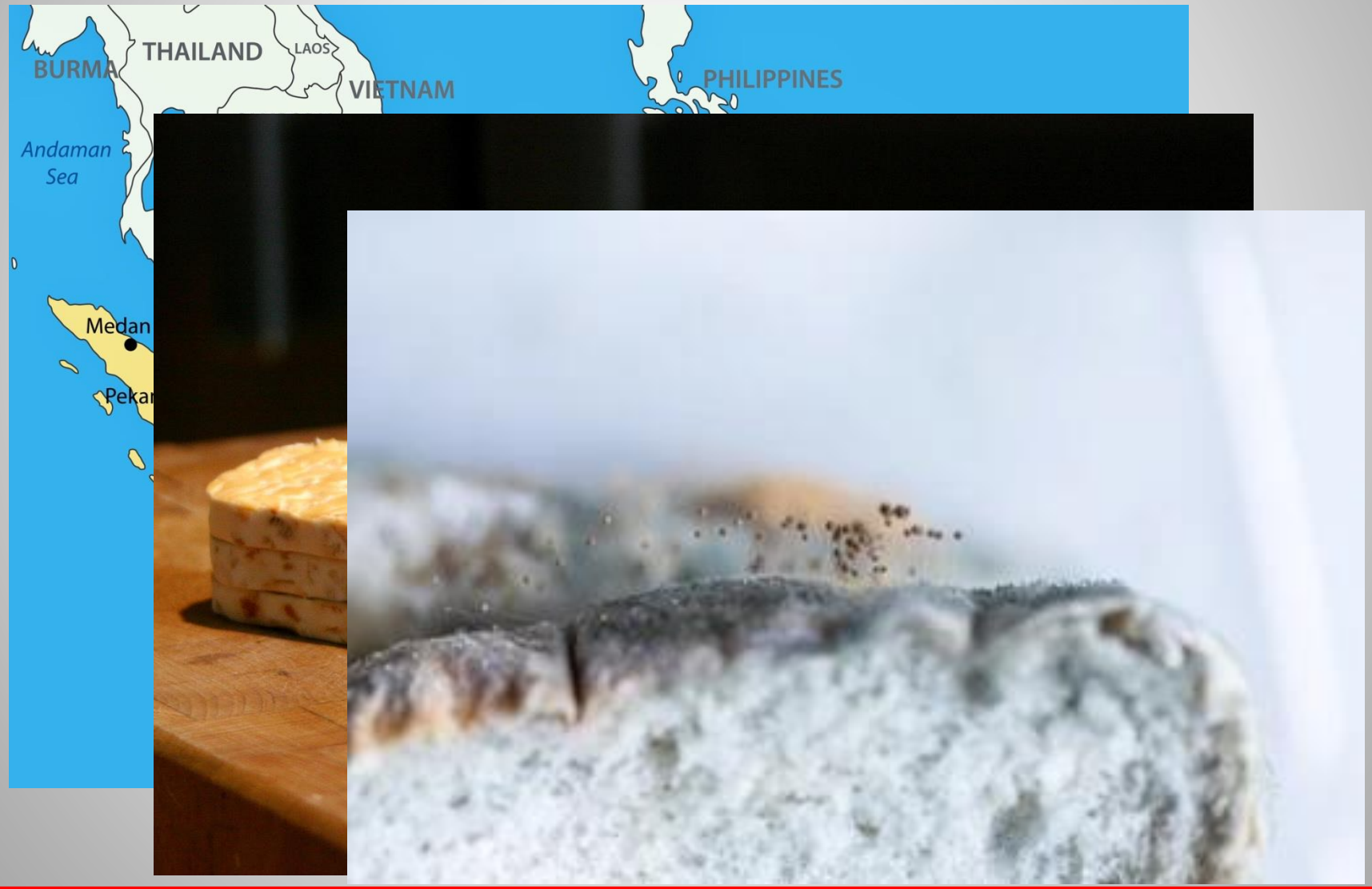
Zorlu Mantar Enfeksiyonları:

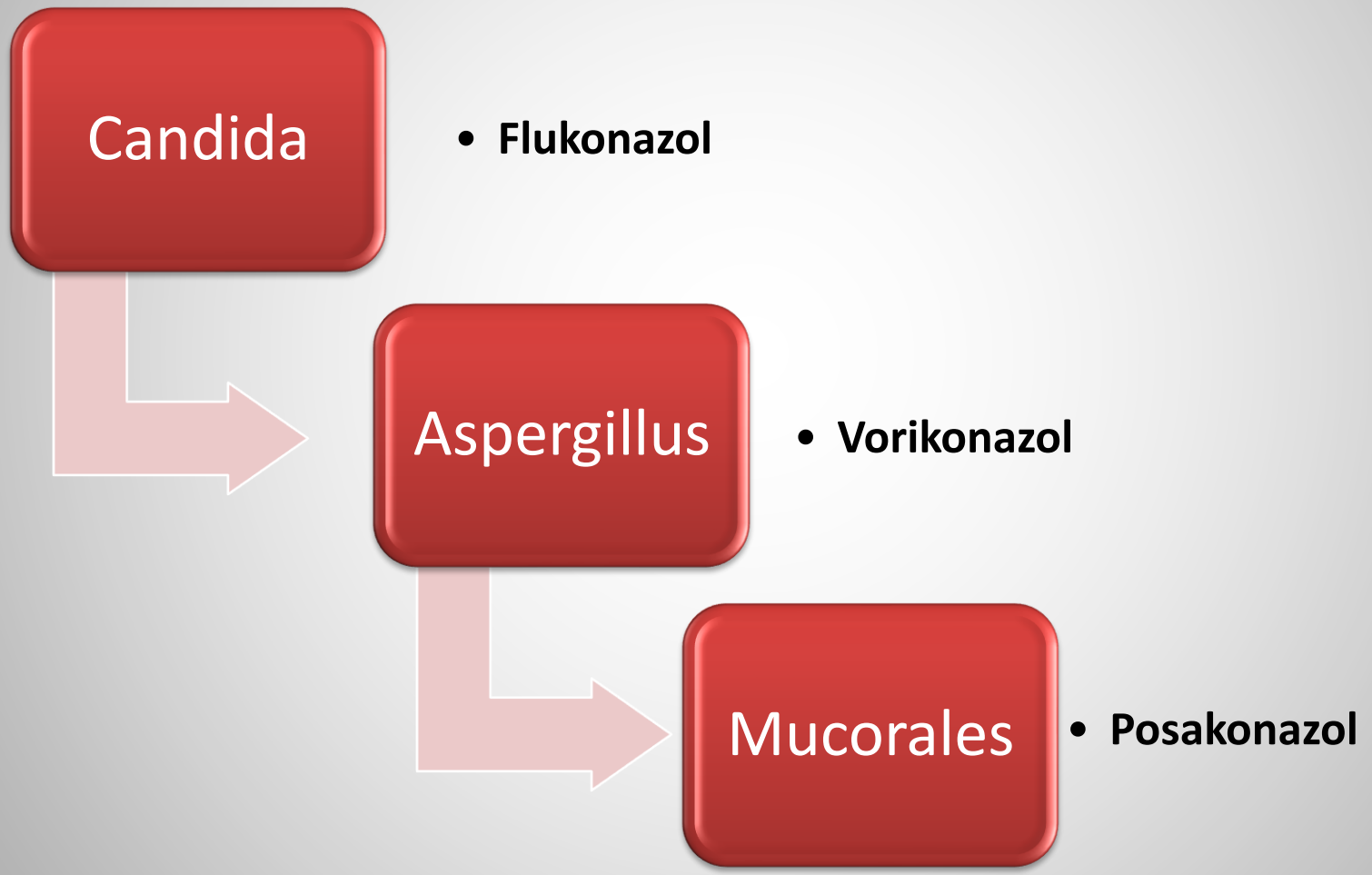
Rhizopus Türleri

Dr Ayşe Özlem METE
Gaziantep Üniversitesi Tıp Fak
Enf Hast ve Klin Mik ABD

Kimdir Rhizopus?

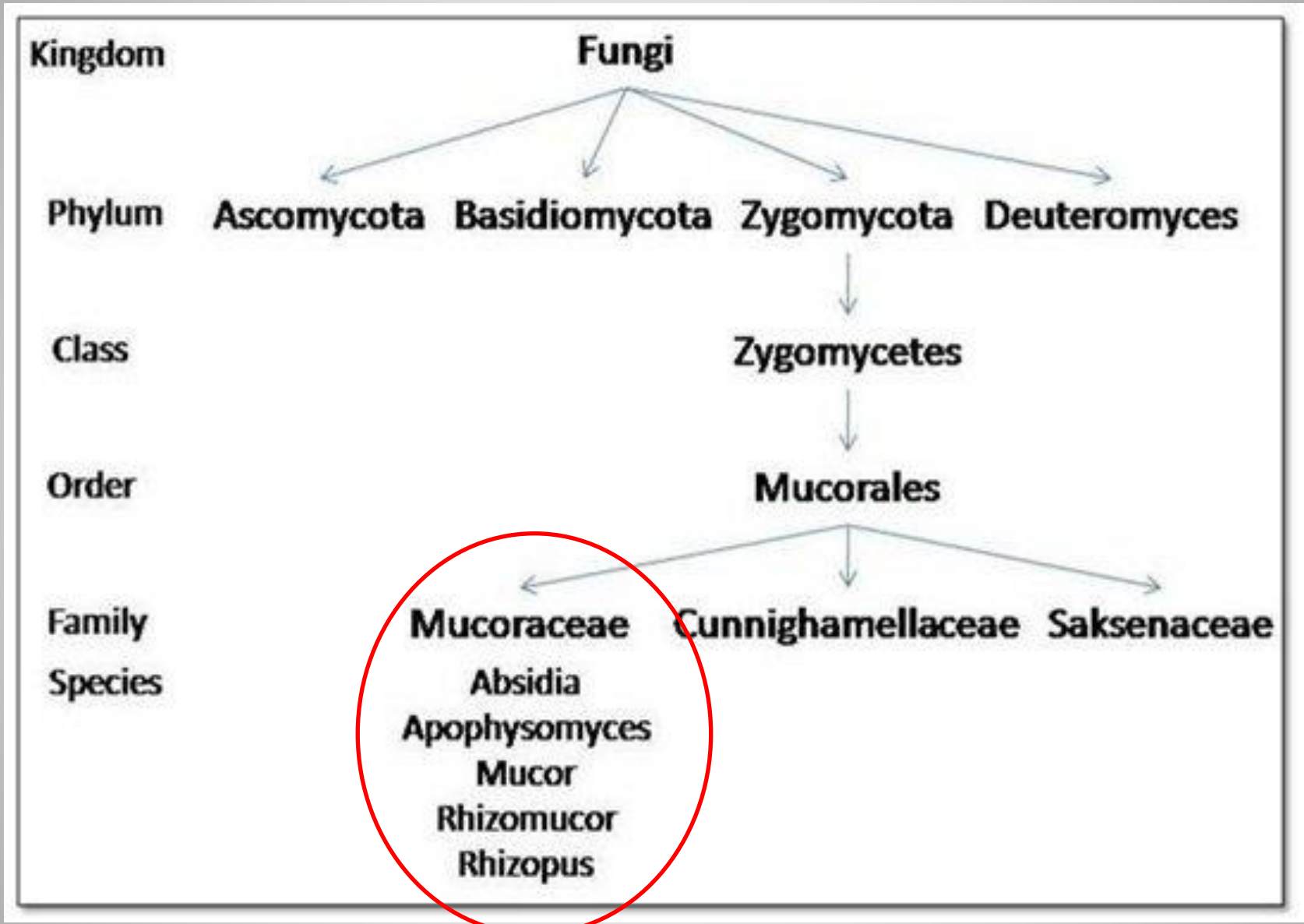


İmmünsüprese Hastalarda



Mantarlar:

Phycomycetes (Lower Fungi)	Ascomycetes (Sac Fungi)	Basidiomycetes (Club Fungi)	Deuteromycetes (Fungi imperfecti)
• Saprolegnia	• Yeast	• Agaricus	• Cercospora
• Rhizopus	• Aspergillus	• Polyporus	• Collectotrichum
• Mucor	• Pencillium	• Puccinia	• Trichoderma
• Albugo	• Neurospora	• Ustilago	• Pyricularia
• Pythium	• Peziza	• Lycoperdon	• Fusarium


Kingdom
Fungi
Phylum
Ascomycota
Basidiomycota
Zygomycota
Deuteromyces
Class
Zygomycetes
Order
Mucorales
Family
Mucoraceae
Cunnighamellaceae
Saksenaceae
Species
Absidia
Apophysomyces
Mucor
Rhizomucor
Rhizopus

Phylogenetic and Phylogenomic Definition of *Rhizopus* Species

Andrii P. Gryganskyi,*,[1] Jacob Golan,[†] Somayeh Dolatabadi,[§§§§,2] Stephen Mondo,[§] Sofia Robb,**
Alexander Idnurm,[††] Anna Muszewska,[‡‡] Kamil Steczkiewicz,[§§] Sawyer Masonjones,** Hui-Ling Liao,***
Michael T. Gajdeczka,* Felicia Anike,[†††] Antonina Vuek,[‡‡‡] Iryna M. Anishchenko,[§§§] Kerstin Voigt,****
G. Sybren de Hoog,[‡] Matthew E. Smith,[††††] Joseph Heitman,[‡‡‡‡] Rytas Vilgalys,* and
Jason E. Stajich**

G3 Genes | Genomes | Genetics
Volume 8 | June 2018 | 2007

Table 1 Census of *Rhizopus* taxa in three major culture collections and the NCBI databases (as of May 5, 2017). The four species with the greatest number of identified isolates are shown in bold

Species	ATCC	Westerdijk Institute (CBS-KNAW)	CABI	GenBank records[a]	PubMed records
R. arrhizus	**137**	**76[b]**	**39[b]**	**7,451[b]**	**2133[b]**
R. caespitosus	—	1	—	14	15
R. circinans	7	—	—	12	11
R. delemar	**-[c]**	**12**	**-**	**2,824**	**155**
R. homothallicus	2	2	6	23	34
R. lyococcus	—	3	—	8	4
R. microsporus[d]	**70**	**48**	**29**	**3,645**	**527**
R. niveus	1	—	—	72	127
R. schipperae	2	1	—	27	14
R. sexualis	3	3	4	39	19
R. stolonifer	**30**	**18[e]**	**14**	**299**	**413**
Rhizopus sp.[f]	1	3	—	269	4182

[a] - Including all genes.
[b] - Including *R. arrhizus* and *R. arrhizus var. delemar*.
[c] - Together with *R. arrhizus*.
[d] - Including *R. azygosporus* and *R. oligosporus*.
[e] - Including *R. stolonifer var. reflexus*.
[f] – Not identified to the species level.

Moleküler filogenetik sınıflama

- *R. Caespitosus*
- *R. Delemar*
- *R. Homothallicus*
- *R. Microsporus*
- *R. arrhizus* (*R. oryzae*)
- *R. Reflexus*
- *R. Schipperae*
- *R. stolonifer.*

Bunlardan sadece **2** tanesi klinik öneme sahiptir.

Abe *et al.* (2010)

Rhizopus arrhizus

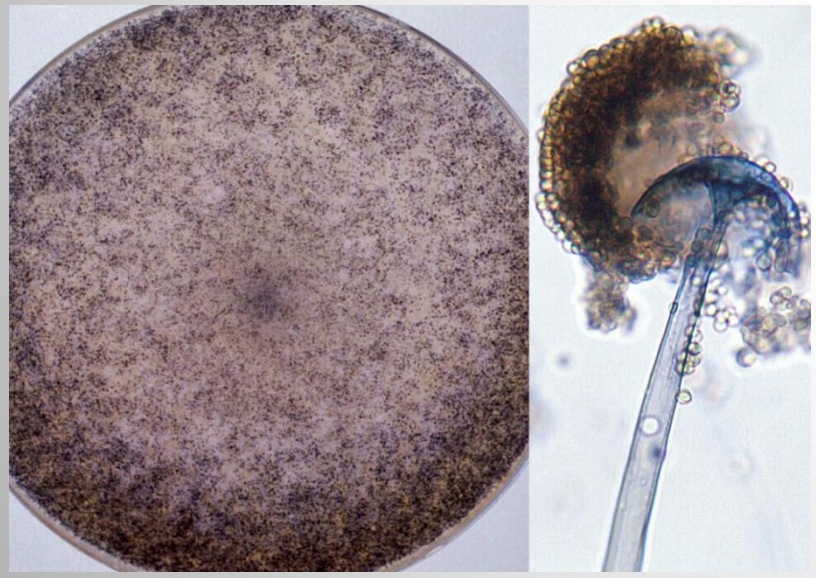
Sinonim:

Rhizopus oryzae

Morfoloji

Koloniler : beyaz pamuk- kahve rengi-gri

40 ^{o}C'de ideal üreme ; 45 ^{o}C 'de ürme yok



Rhizopus arrhizus'un kültür ve sporangiaspor görüntüsü.

Rhizopus arrhizus'un sporangiophore, rhizoid ve sporangia

Rhizopus microsporus:

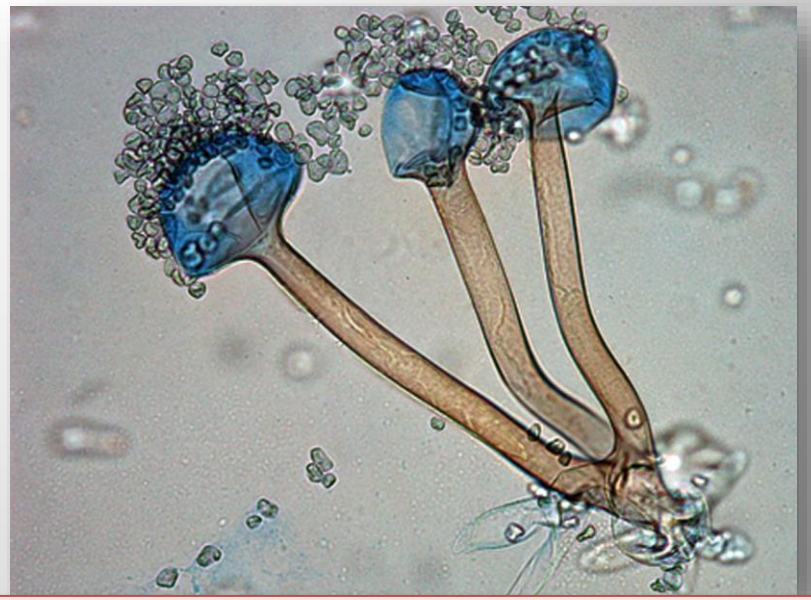
- Sinonim:

  Rhizopus azygosporus;

  - Rhizopus microsporus var. microsporus
  - Rhizopus microsporus var. oligosporus
  - Rhizopus microsporus var. rhizopodiformis
  - Rhizopus microsporus var. chinensis

- Gri koloni
- 45 °C'de iyi ürer

  50-52 °C'de üreyebilir



Rhizopus microsporus sporangia showing sporangiospores, columellae, sporangiophores and rhizoids.

Antifungal susceptibility: *Rhizopus arrhizus* (Australian national data); MIC µg/mL.

Antifungal	No	<0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	≥64
AMB	35		4	12	14	4		1					
ISAV	6				1		1	2					
VORI	34							1	2	10	16	5	
POSA	33					6	10	11	6				
ITRA	35		1		4	9	8	6		1	6		

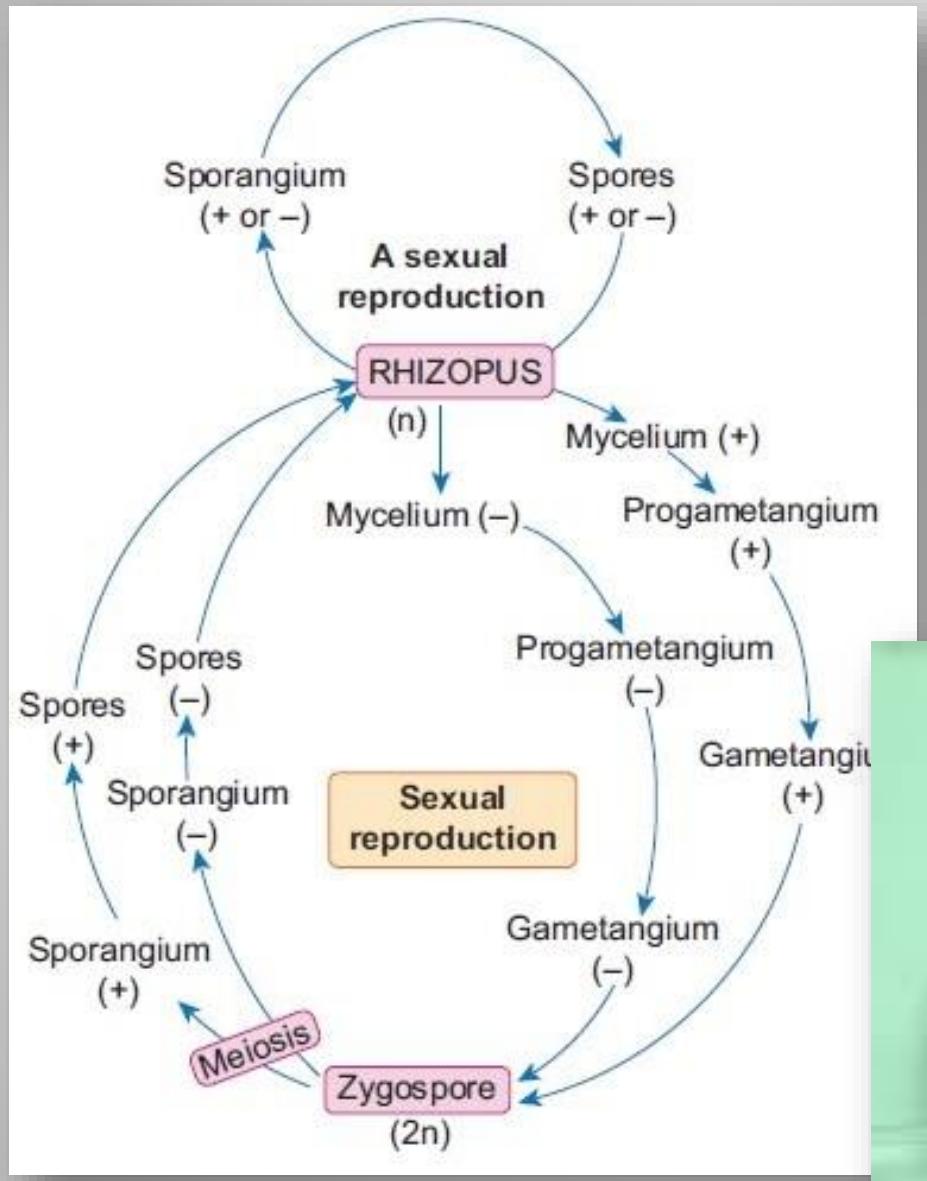
Antifungal susceptibility: *Rhizopus microsporus* (Australian national data); MIC µg/mL.

Antifungal	No	<0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	≥64
AMB	98								3	27	65	3	
ISAV	6						1	4		1			
VORI	98			12	29	40	11	5	1				
POSA	98			3	10	48	27	9		1			
ITRA	98			1	3	23	49	6	4		11		1

Bu 2 etken mukormikoz olgularının >%60' ından sorumlu

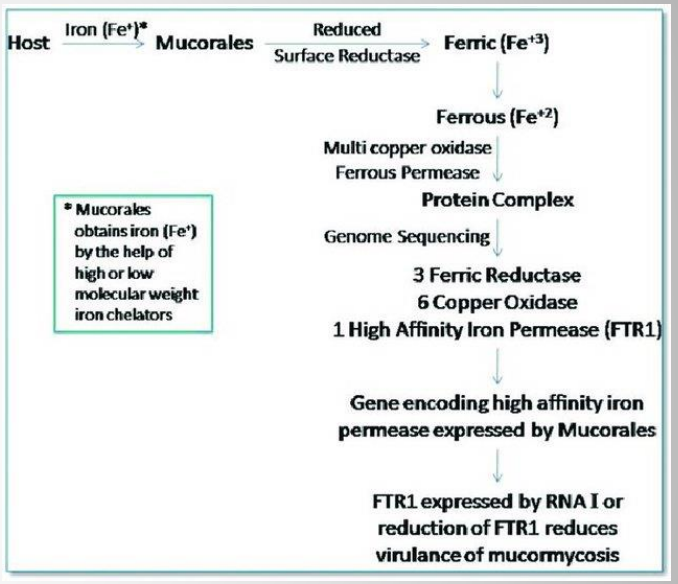
Mukormikoz

- «Kara Ölüm»
- «Zombi Hastalığı»
- Murocales takımından mantarlar
- Akut/Subakut


Sporangium
(+ or –)
Spores
(+ or –)
A sexual
reproduction
RHIZOPUS
(n)
Mycelium (+)
Mycelium (–)
Progametangium
(+)
Progametangium
(–)
Gametangium
(+)
Spores
(–)
Spores
(+)
Sporangium
(–)
Sexual
reproduction
Gametangium
(–)
Sporangium
(+)
Meiosis
Zygospore
(2n)

Virülans:

- FTR1
- Keton redüktaz enzimi
- ADP-ribosylation factor
- Rhizopus proteaz enzimi
- Calcineurin
- Serine ve aspartate protease
- Makrofaj fonksiyonlarını bozar



Mukormikozis risk faktörleri:

- Diabetes Mellitus (özellikle ketoasidoz)
- Glukokortikoid tedavisi
- Hematolojik maligniteler
- HSCT
- SOT
- Deferoksamin tedavisi
- Demir aşırı yüklenmesi
- AIDS
- IV madde bağımlıları
- Travma/yanık
- Malnutrisyon

- Keton redüktaz:

yüksek glukoz ve asidik ortamda çoğalma

Studies of Opportunistic Fungi. I. Inhibition of *Rhizopus oryzae* by Human Serum.

Author(s) : Gale, G. R. ; Welch, Ann M.

Journal article : American Journal of Medical Sciences 1961 Vol.241 No.5 pp.604-12 ref.13

Abstract : This work was prompted by the previous observations of others of the fungistatic properties of human serum and the organism selected for study was *Rhizopus oryzae* from a fatal human case of cerebral mucormy-cosis. Serum was collected from routine blood donors, umbilical cords of newly born babies and 6 diabetics (4 well controlled, 1 in acidosis and 1 recently dead of widespread carcinoma)

Mukormikozis risk faktörleri:

- Diabetes Mellitus (özellikle ketoasidoz)
- Glukokortikoid tedavisi
- Hematolojik maligniteler
- HSCT
- SOT
- Deferoksamin tedavisi
- Demir aşırı yüklenmesi
- AIDS
- IV madde bağımlıları
- Travma/yanık
- Malnutrisyon

- FTR-1
- Deferoksamin-Demir Şelatörleri
- Demir yüklemesi

Kidney International, Vol. 45 (1994), pp. 667–671

Deferoxamine augments growth and pathogenicity of *Rhizopus*, while hydroxypyridinone chelators have no effect

JOHAN R. BOELAERT, JAN VAN CUTSEM, MARIELLE DE LOCHT, YVES-JACQUES SCHNEIDER, and ROBERT R. CRICHTON

Mukormikozis risk faktörleri:

- Diabetes Mellitus (özellikle ketoasidoz)
- Glukokortikoid tedavisi
- Hematolojik maligniteler
- HSCT
- SOT
- Deferoksamin tedavisi
- Demir aşırı yüklenmesi
- AIDS
- IV madde bağımlıları
- Travma/yanık
- Malnutrisyon
- **COVID-19**

Infection (2021) 49:833–853
https://doi.org/10.1007/s15010-021-01670-1

REVIEW

COVID-19 and mucor

Jaffar A Al-Tawfiq[1,2,3,21], Saa
Abbas
Salma

Mycopathologia (
https://doi.org/10.

CASE REPO

Coronavi
(CAM):

Dee
Har
Rite

- % 85 DM
- % 29 Ketoasidoz
- % 85 Glukokortikoid kullanımı
- %87 Geniş spektrumlu antibiyotik kullanımı
- Mortalite: % 33
- Klinik: % 42 Rino-orbital
- Etken tür: % 85 Rhizopus spp

Received: 1
DOI: 10.111

REVIEW ARTICLE

WILEY

COVID-19-associated mucormycosis: An updated systematic review of literature

Rimesh Pal[1] | Birgurman Singh[2] | Sanjay Kumar Bhadada[1] | Mainak Banerjee[3] | Ranjitpal Singh Bhogal[4] | Neemu Hage[5] | Ashok Kumar[6]

Klinik

Kimde?

- Rino-Orbito-serebral
  - DM
  - % 25-62 mortal
- Pulmoner/ Disemine
  - Hematolojik maligniteler, HSCT, SOT
  - %48-87 mortal
- Cilt
  - İmmünkompetan/immünkompromize
  - Travma , yanık, afetler
- GIS
  - …….
  - prematürite

Dissemine olgularda mortalite %90-100

Tanı:

Yaklaşım, klinik forma göre değişir

- Histopatoloji:
  - Tipik hif-fungal elemanların görülmesi
  - (septasız hiflerden oluşan sönositik miçeller)
  - Anjio-invazyon, doku nekrozu
- Mikrobiyoloji:
  - 24-48 saatte tüm petri kutusunu kaplar
  - Negatif sonuç için 5-6 gün beklenmeli
- Görüntüleme:
  - Toraks CT aspergillus???
    - Ters Halo
  - Plevral effüzyon, nodüler infiltrasyon,
- Biyobelirteçler:
  - Galaktomannan
  - 1,3 Beta-D-Glukan

Pozitif → Aspergillus spp.

Negatif → Zygomyces

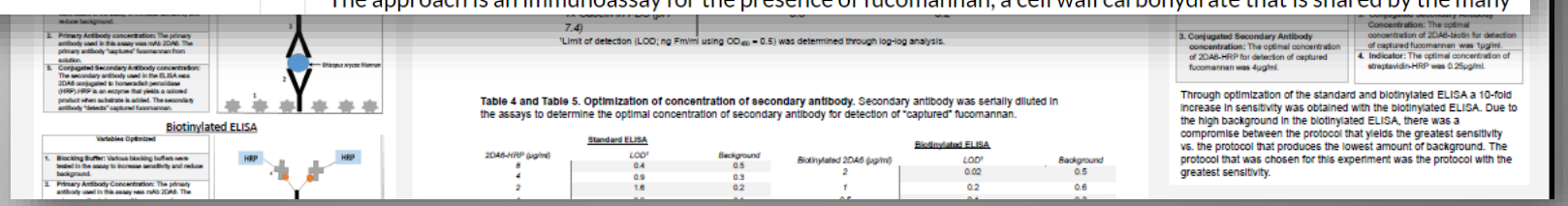
28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

Immunoassay for early diagnosis of mucormycosis

Burnham-Marusich, Amanda Rose Kozel, Thomas R.
Dxdiscovery, Inc., Reno, NV, United States

Abstract

Mucormycosis is one of the deadliest of the invasive fungal infections. Mucormycosis occurs most often in patients with hematological malignancies undergoing chemotherapy, patients who have received hematopoietic stem cell transplants or patients with diabetes mellitus. Improved diagnosis is the most frequently noted unmet need for management of the mucormycosis patient. Delays in treatment increase the mortality rate from an already high 47% to 83%. Unlike other invasive fungal infections, there has been no known fungal biomarker for diagnosis of mucormycosis. However, in our preliminary studies, a monoclonal antibody (mAb 2DA6) was produced that has high reactivity with cell wall fucomannan of the Mucorales. A first-generation immunoassay produced from mAb 2DA6 found fucomannan in serum, urine, broncho alveolar fluid and infected tissue from clinically relevant mouse models of mucormycosis and in plasma and urine from human cases of mucormycosis. The goal is an immunoassay that uses plasma or urine to rapidly diagnose early-stage mucormycosis. The target population is individuals for whom diabetes mellitus or use of potent immunosuppressive drugs has led to a dramatic increase in the occurrence of mucormycosis. The approach is an immunoassay for the presence of fucomannan, a cell wall carbohydrate that is shared by the many



- **Tür tayini:**
  - %10 KOH
  - Mikroskopik görünümü
  - Koloni morfolojisi
  - Karbonhidrat asimilasyonu
  - Termotolerans
  - Moleküler yöntemler***
    - PCR
    - RFLP
  - BAL elverişli değil
  - İnce iğne aspirasyon sitolojisi

Tedavi:

- Erken tanı
- Hızlı antifungal
  - Amfoterisin-B
  - Posakonazol
  - İsavukonazol
- Geniş-agresif debridman
- Predispozan risk faktörünün ortadan kaldırılması
  - Kan glukoz düzeyinin normalizasyonu
  - İmmunsupresyonun azaltılması
  - Deferoksamin yerine defarasirox veya deferiprone

Antifungal Tedavi:

- AmB → lipozomal / lipid kolloidal
- Böbrek/Üriner Tutulumu → Konvansiyonel
- Kombinasyon Tedavisi: Anektodal*
  - AmB + Posakonazol / İsavukonazol
  - AmB + Ekinokandin (*R. orzea*)
- Step Down Tedavi:

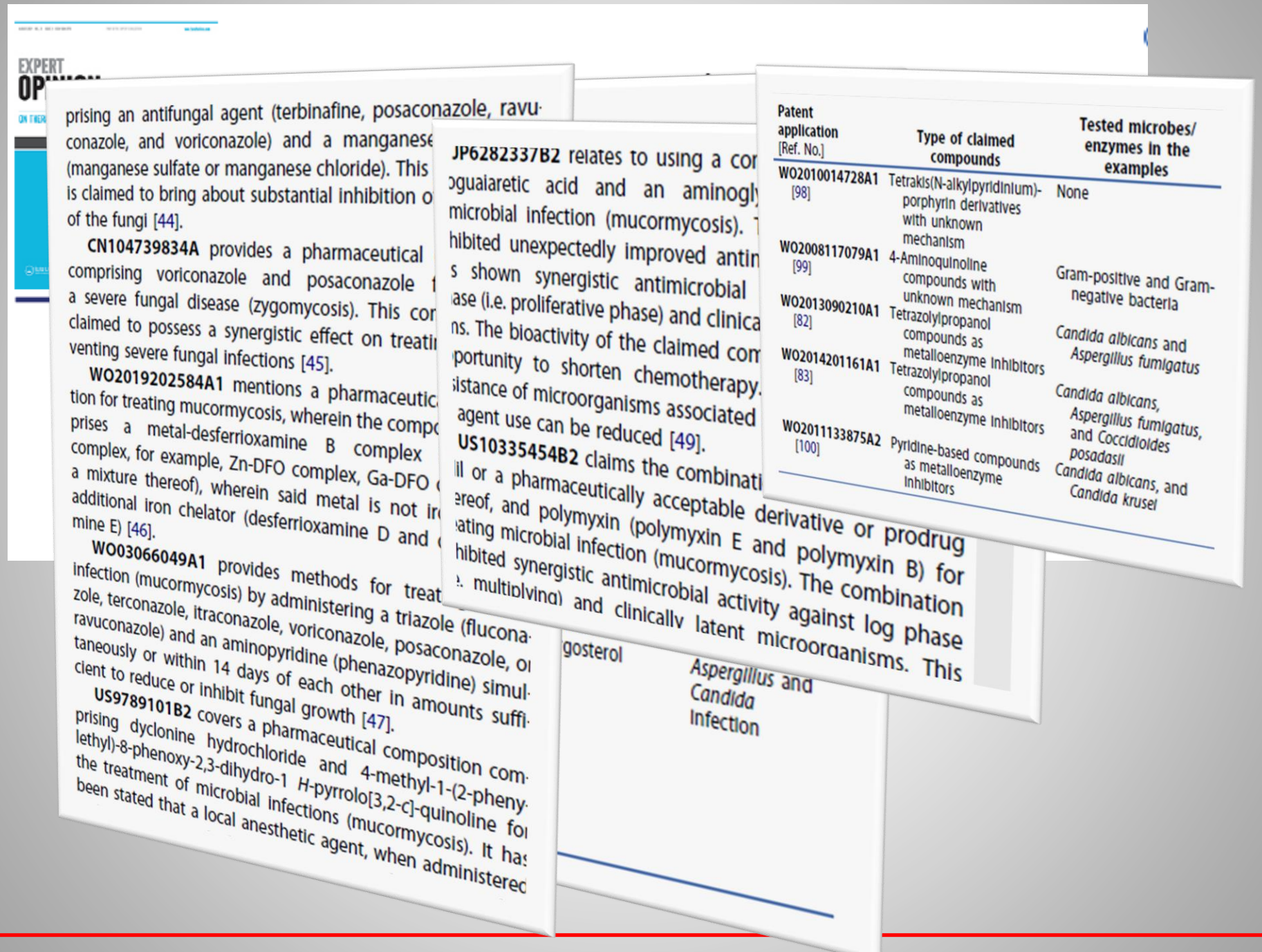
  AmB IV semptomlar gerileyene kadar
  - Ardından Posakonazol PO / Isavukonazol PO*
  - 5mg/kg haftada 3 kez hatta 2 kez IV AmB (alternatif)**
- Kurtarma Tedavisi

**Antimicrob Agents Chemother.* 2008;52:1556–1558
**Drugs. 2016 Mar; 76(4): 485–500.

ESCIL-3

	Amphotericin B % with MIC ≤1 μg/mL	Posaconazole % with MIC ≤0.5 μg/mL	Itraconazole % with MIC ≤0.5 μg/mL
Rhizopus sp (101)	100	80	62
Rhizopus arrhizus (20)	100	64	50
Rhizopus microsporus (12)	100	78	60
Mucor sp. (41)	94	70	57
Mucor circinelloides (6)	100	0	0
Rhizomucor sp.(5)	100	67	67
Lichtheimia sp. (3)	100	100	50
Lichtheimia corymbifera (9)	100	100	100
Cunninghamella sp. (13)	63	75	29
Apophysomyces elegans (6)	100	83	80

Modified from Almyroudis 2007.[20]



prising an antifungal agent (terbinafine, posaconazole, ravu-
conazole, and voriconazole) and a manganese
(manganese sulfate or manganese chloride). This
is claimed to bring about substantial inhibition o
of the fungi [44].

CN104739834A provides a pharmaceutical
comprising voriconazole and posaconazole
a severe fungal disease (zygomycosis). This cor
claimed to possess a synergistic effect on treati
venting severe fungal infections [45].

WO2019202584A1 mentions a pharmaceutic
tion for treating mucormycosis, wherein the compo
prises a metal-desferrioxamine B complex
complex, for example, Zn-DFO complex, Ga-DFO
a mixture thereof), wherein said metal is not ir
additional iron chelator (desferrioxamine D and
mine E) [46].

WO03066049A1 provides methods for treat
infection (mucormycosis) by administering a triazole (flucona-
zole, terconazole, itraconazole, voriconazole, posaconazole, o
ravuconazole) and an aminopyridine (phenazopyridine) simul-
taneously or within 14 days of each other in amounts suffi-
cient to reduce or inhibit fungal growth [47].

US9789101B2 covers a pharmaceutical composition com-
prising dyclonine hydrochloride and 4-methyl-1-(2-pheny-
lethyl)-8-phenoxy-2,3-dihydro-1 *H*-pyrrolo[3,2-*c*]-quinoline fo
the treatment of microbial infections (mucormycosis). It has
been stated that a local anesthetic agent, when administered

JP6282337B2 relates to using a cor
ogualaretic acid and an aminogly
microbial infection (mucormycosis).
hibited unexpectedly improved antin
s shown synergistic antimicrobial
ase (i.e. proliferative phase) and clinica
ns. The bioactivity of the claimed com
portunity to shorten chemotherapy.
sistance of microorganisms associated
agent use can be reduced [49].

US10335454B2 claims the combinati
il or a pharmaceutically acceptable derivative or prodrug
ereof, and polymyxin (polymyxin E and polymyxin B) for
ating microbial infection (mucormycosis). The combination
hibited synergistic antimicrobial activity against log phase
. multiplying) and clinically latent microorganisms. This

gosterol

Aspergillus and
Candida
infection

Patent application [Ref. No.]	Type of claimed compounds	Tested microbes/ enzymes in the examples
WO2010014728A1 [98]	Tetrakis(N-alkylpyridinium)-porphyrin derivatives with unknown mechanism	None
WO2008117079A1 [99]	4-Aminoquinoline compounds with unknown mechanism	Gram-positive and Gram-negative bacteria
WO2013090210A1 [82]	Tetrazolylpropanol compounds as metalloenzyme inhibitors	*Candida albicans* and *Aspergillus fumigatus*
WO2014201161A1 [83]	Tetrazolylpropanol compounds as metalloenzyme inhibitors	*Candida albicans*, *Aspergillus fumigatus*, and *Coccidioides posadasii*
WO2011133875A2 [100]	Pyridine-based compounds as metalloenzyme inhibitors	*Candida albicans*, and *Candida krusei*

Ek Tedaviler:

- Hiperbarik oksijen ???
  - Fungusidal
  - Nötrofil fagositozunu arttırır
  - Anjiogenezi arttırır/iyileştirir
- GCSF / GMCSF
  - Hayvan çalışmaları başarılı
  - İnsan çalışmaları henüz sınırlı sayıda olgu
- IFN-γ

Received: 11 January 2021 | Revised: 11 April 2021 | Accepted: 27 April 2021

DOI: 10.1002/ccr3.4290

CASE REPORT

Clinical Case Reports Open Access WILEY

Rhizopus microsporus typhlitis in a patient with acute myelogenous leukemia

Marcus Trybula[1] | Diping Wang[2] | Lauren Baumann[3] | Timothy A. Pritts[3] | Bryan C. Hambley[4]

monocytic differentiation. Intensive induction chemotherapy with cytarabine and daunorubicin along with prophylactic cefepime, micafungin, and acyclovir was initiated.

Oral intake was restricted and antimicrobials were broadened to meropenem plus isavuconazole (later switched to amphotericin secondary to hyperbilirubinemia).

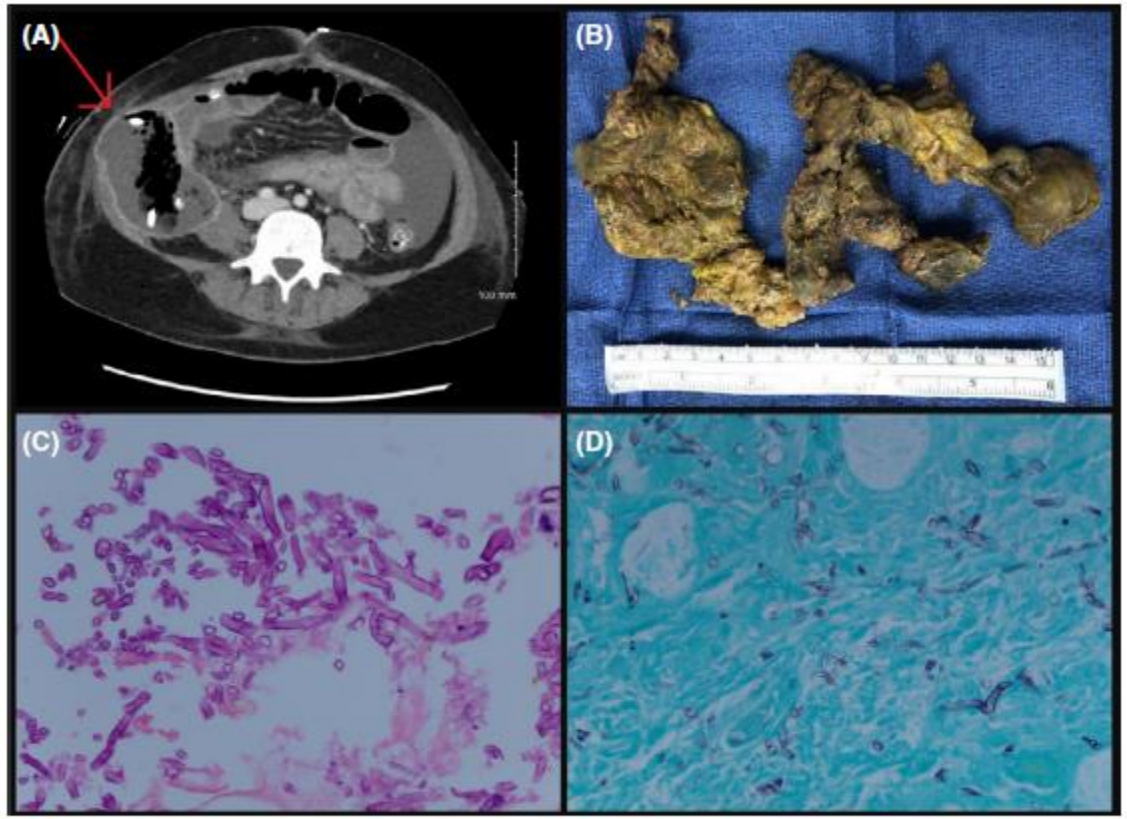


FIGURE 1 *Rhizopus* Typhlitis. A, Axial computed tomography image of the abdomen. Typhlitis with superimposed right abdominal wall abscess/necrotic collection (red arrow) B, Necrotic tissue with superimposed fungal infection C, 400x H&E stain of tissue show broad-based, ribbonlike, nonseptate hyphae consistent with *Rhizopus microsporus*. D, 400x GMS stain highlighting presence of *Rhizopus microsporus*

Open Access Case Report

DOI: 10.7759/cureus.16210

Pulmonary Mucormycosis: An Interesting Case of Rhizopus Mucormycosis

Chijioke D. Ukoha Jr. [1] , Nicholas Nguyen [1]

1. Internal Medicine, Methodist Dallas Medical Center, Dallas, USA

Corresponding author: Chijioke D. Ukoha Jr., cjukoha@gmail.com

Abstract

We report a case of a 57-year-old Vietnamese gentleman who presented with chest pain and shortness of breath for four weeks. The patient had a history of diabetes mellitus and kidney transplant in the past year and was currently on immunosuppressive agents. The patient's condition worsened despite broad-spectrum antibiotics, so amphotericin was added. Further evaluation with bronchoscopy and transbronchial biopsy was suggestive of *Rhizopus* mucormycosis. Despite antifungal therapy, his condition worsened, resulting in multi-organ failure and eventual mortality.

Categories: Internal Medicine, Infectious Disease, Pulmonology
Keywords: pulmonary, mucormycosis, rhizopus, mucor, zygomycosis

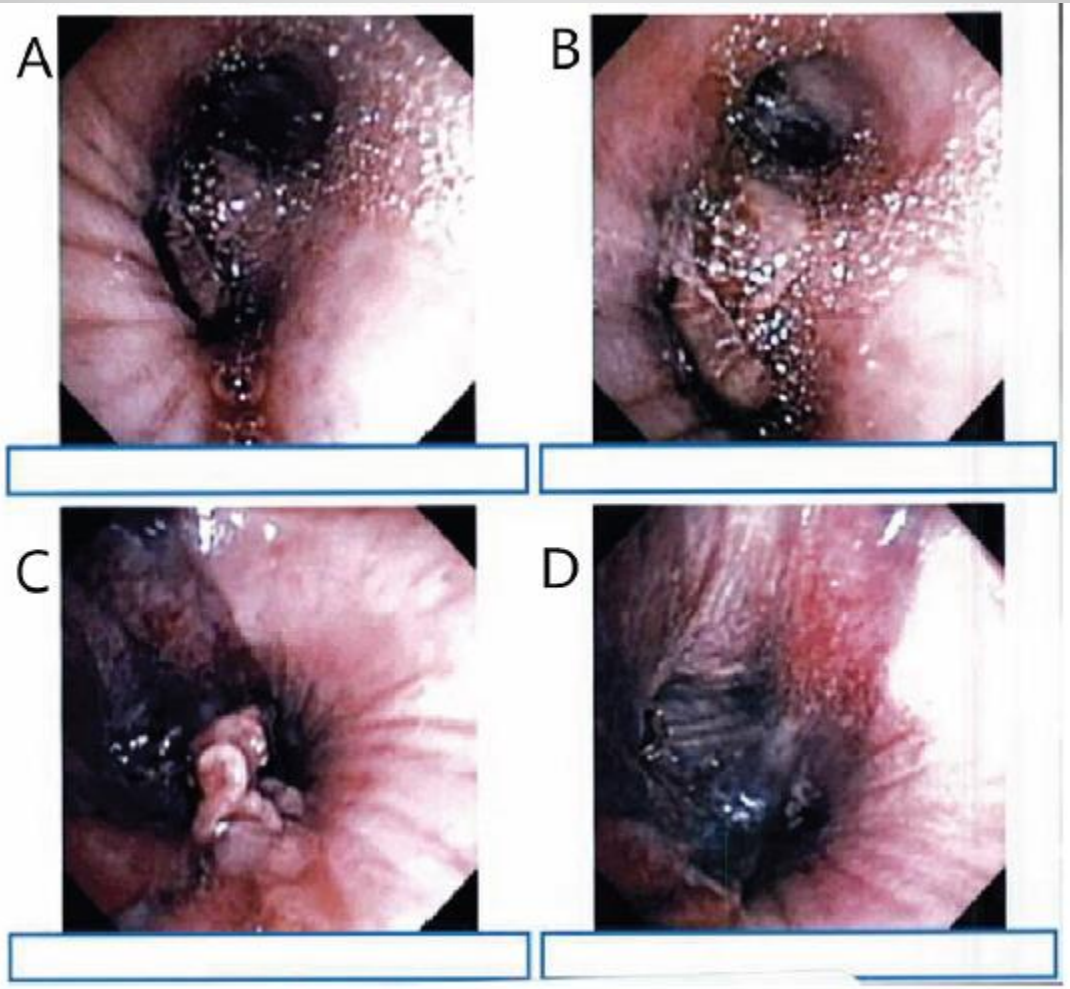


FIGURE 1: Bronchoscopy depicting necrotizing tissue concerning for pulmonary mucormycosis

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2021 December 16; 9(35): 11108-11114

DOI: 10.12998/wjcc.v9.i35.11108

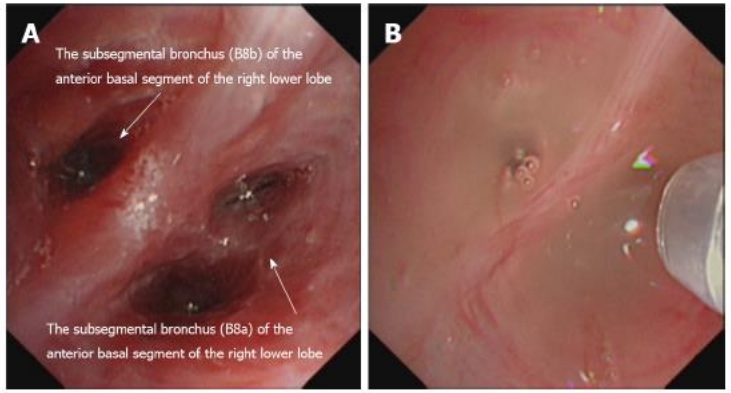
ISSN 2307-8960 (online)

CASE REPORT

Rhizopus microsporus lung infection in an immunocompetent patient successfully treated with amphotericin B: A case report

Long Chen, Yuan Su, Xian-Zhi Xiong

Core Tip: We present the case of a 19-year-old girl who developed *Rhizopus microsporus* (*R. microsporus*) lung infection without any known immunodeficiency. Due to the early detection of the *R. microsporus* in bronchoalveolar lavage fluid by metagenomics next generation sequencing, promptly anti-mucor therapy was started. A new attempt of a combination therapy of intravenous, inhalation, and local airway perfusion of amphotericin B was then performed, which showed a good therapeutic effect.



30 gün AmB
80. Güne kadar Posakonazol PO

(ÇİN)

Figure 2 Images in electronic bronchoscopy. A: The anterior basal branch was swollen, accompanied by a deformed and narrowed lumen of the anterior basal branch; B: Perfusion with amphotericin B (10 mg dissolved in 10 mL saline) on the anterior basal segment of the right lower lobe was performed through a microtube in an electronic bronchoscope.

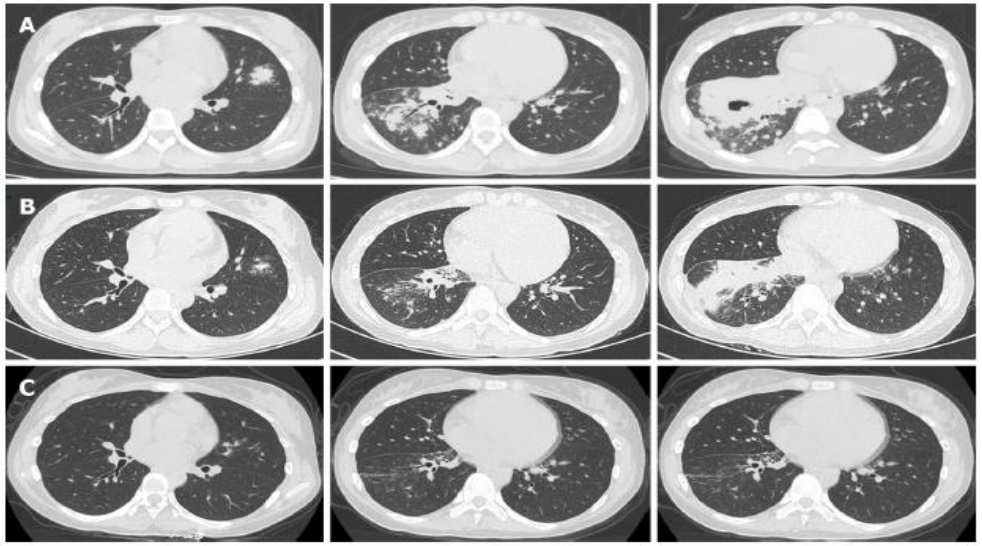


Figure 3 Computed tomography images. A: Thoracic computed tomography (CT) images showing bilateral pulmonary infection with cavitation in the right lower lobe upon arrival; B: After 30 d of antifungal treatment, chest CT showed a decrease in lung inflammation and an absorption of cavitation in the right lower lobe; C: Chest CT follow-showed that lung inflammation dissipated after 80 d.


CHALLENGE
CHALLENGE
CHALLENGE



©taylor F. Lockwood