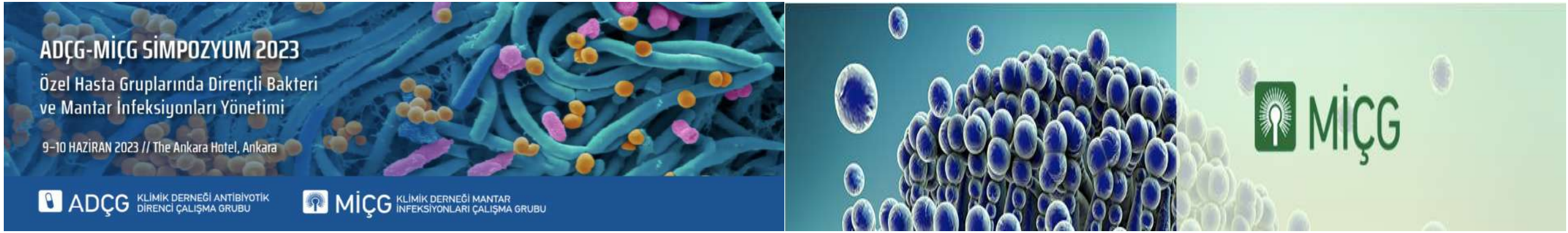


COVID-19 Sonrası Diğer Fungal İnfeksiyonlarda Değişenler

Yasemin Tezer Tekçe

Sunum planı

- COVID-19 sürecinde invaziv fungal infeksiyonlar
- COVID-19 ilişkili mukormikoz
- COVID-19 ilişkili kriptokokkoz
- Fusariosis
- Pnömosistis pnömonisi
- COVID-19 ilişkili *Scedosporium*

DSÖ fungal ajanları kritik, yüksek veya orta öncelikli patojenler derecelendirildi:

*Antifungal direnç profilleri,
*Mortalite oranları,
*Kanıta dayalı tanı ve tedavi seçeneklerinin eksikliğine
*Yıllık insidans oranları ve
*Komplikasyon ve sekel durumlarına göre,

Zhao et al. Infectious Diseases of Poverty (2023) 12:20

Fig. 1. WHO fungal priority pathogens list (WHO FPPL)

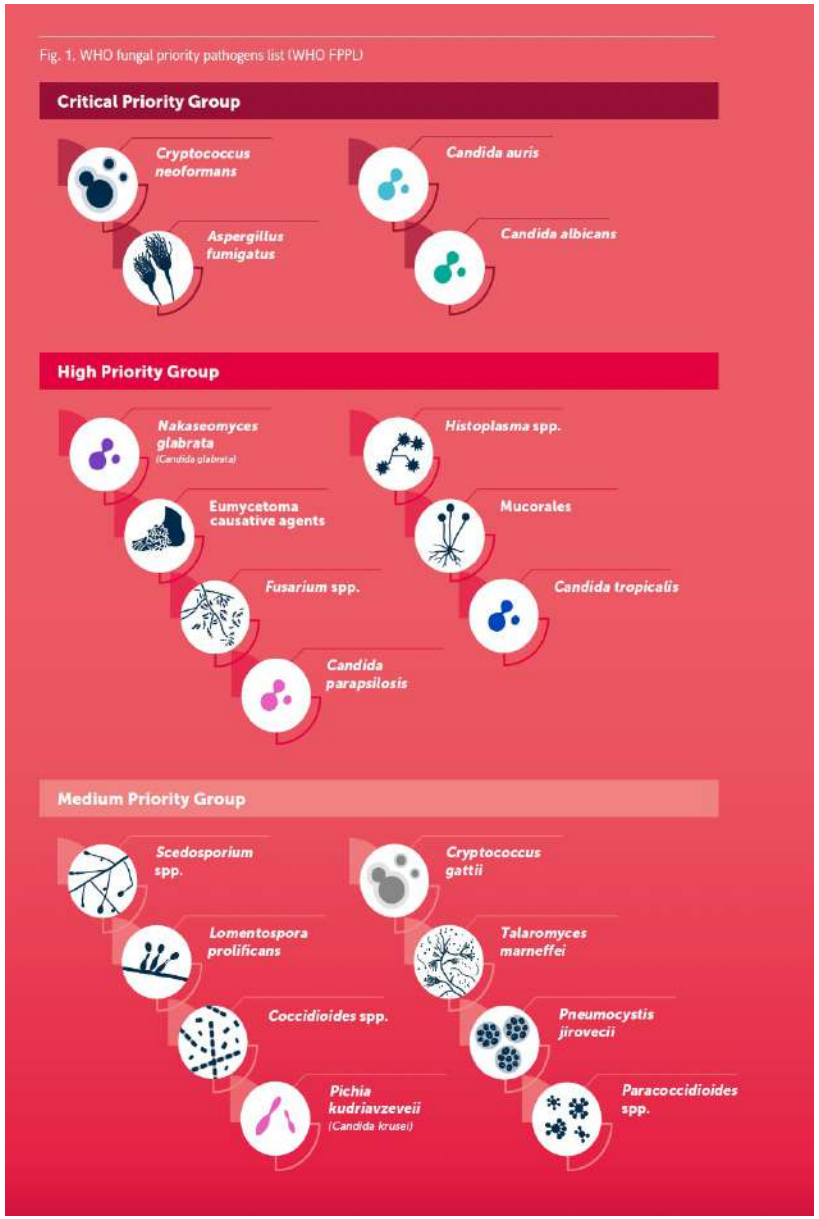
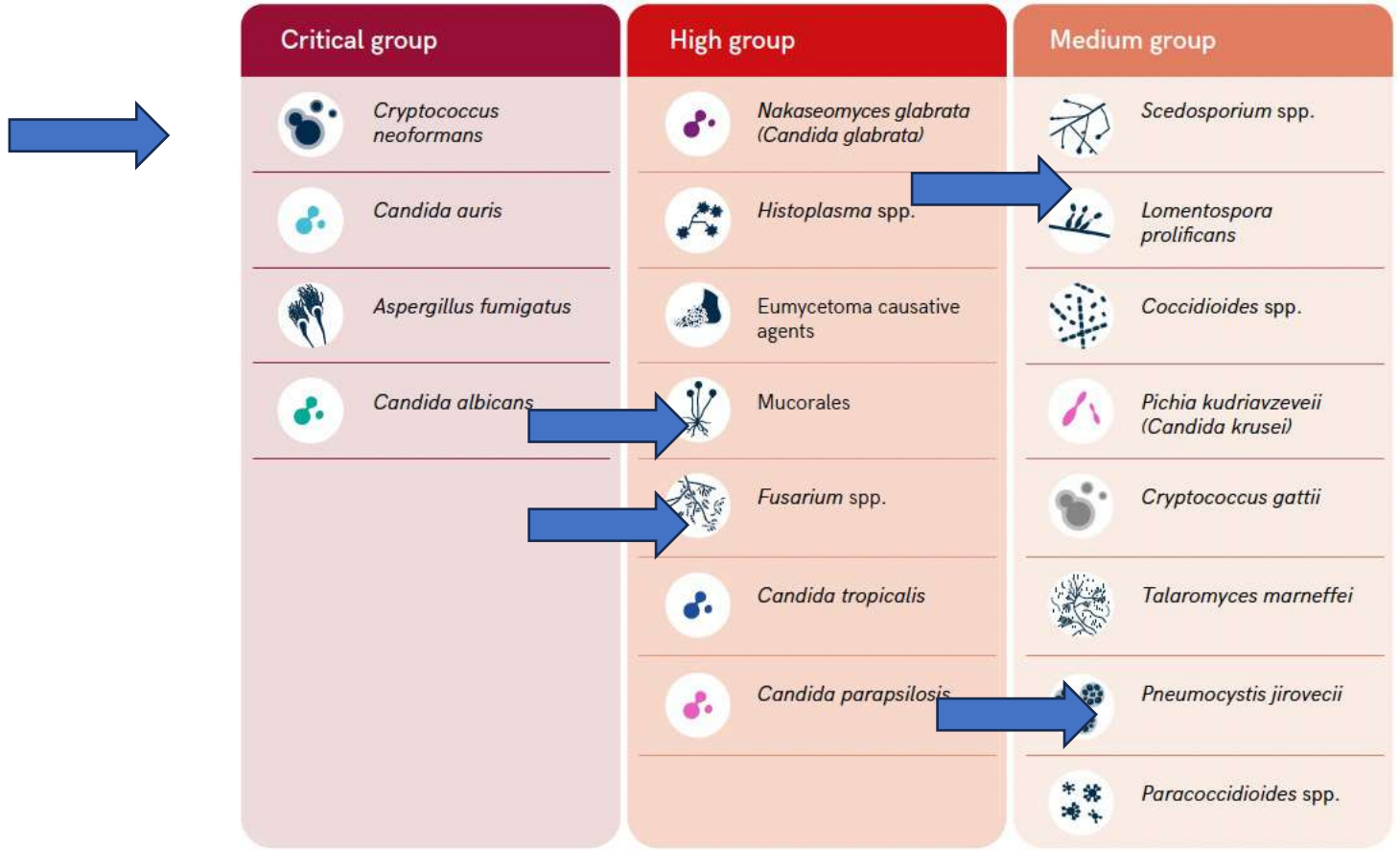


Table 2. Prioritization criteria, definitions and levels

Criterion	Definition/description	Level value
Deaths	Average case fatality rate	**Low:** < 30% **Medium:** 30–70% fatality **High:** > 70% **Unknown:** no reliable data
Annual incidence	Number of new cases per million population each year	**Low:** < 2/million **Medium:** 2–50/million **High:** > 50/million **Unknown:** no data available
Current global distribution	Extent of geographic distribution across the globe	**Localized** in ≤ 2 WHO regions **Globally distributed** in ≥ 3 WHO regions **Unknown:** due to inadequate data
Trends in last 10 years	Evidence of change in incidence/prevalence patterns	**Stable:** no evidence of increasing incidence/prevalence **Increasing:** evidence of increasing incidence/prevalence **Unknown:** due to inadequate data
Inpatient care	Average length of hospital stay required for treatment following initial diagnosis	**Low:** < 2 days **Medium:** 2 days to 2 weeks **High:** > 2 weeks **Unknown:** no data available
Complications and sequelae	Proportion of patients suffering long-term complications of disease	**Low:** expected to affect a minority of patients (e.g. < 10%). **Medium:** expected to affect a significant proportion of patients (e.g. 10–50%). **High:** expected to affect the majority of patients (e.g. > 50%).
Antifungal resistance	Rate (or level) of acquired or intrinsic resistance to antifungal treatment	**Low:** < 10% acquired or intrinsic resistance for all four classes of antifungals. **Medium:** acquired or intrinsic resistance (> 10%) described for agents from one to two classes of antifungals. **High:** acquired or intrinsic resistance (> 10%) described for agents from three to four classes of antifungals. **Unknown:** no reliable data available
Preventability	Transmission/ acquisition dynamics and availability of evidence-based, effective preventive measures	**Low:** transmission/acquisition dynamics well described, and preventive measures ineffective or of low-quality evidence, and/or not widely available or difficult to implement. **Medium:** transmission/acquisition dynamics are not well described, but preventive measures based on moderate or high-quality evidence are available and effective. **High:** transmission/acquisition dynamics are well described, and preventive measures based on moderate or high-quality evidence are universally available and effective. **Unknown:** transmission/acquisition dynamics not well described. No preventive measures described.
Access to diagnostic tests	Availability of diagnostics	**Low:** diagnostics are not available in reference laboratories. **Medium:** diagnostics are available in institutional or reference laboratories but not universally available due to cost, distribution or technical issues. **High:** diagnostics are available and have been successfully implemented in institutional diagnostic laboratories, in at least one but not all high-burden/low-resource settings where disease occurs. **Very high:** diagnostics are universally available in institutional diagnostic laboratories where disease occurs.
Evidence-based treatments	Treatment options are evidence based and accessible	**Very low:** treatment based on expert opinion with limited evidence. **Low:** peer-reviewed, high-quality guidelines available, but first-line treatment options are unaffordable, toxic or unavailable where disease occurs. **Medium:** peer-reviewed, high-quality guidelines with at least one first-line treatment option which is affordable, non-toxic and available where disease occurs. **High:** peer-reviewed, high-quality guidelines with at least one first-line treatment


Critical group
Cryptococcus neoformans
Candida auris
Aspergillus fumigatus
Candida albicans
High group
Nakaseomyces glabrata (Candida glabrata)
Histoplasma spp.
Eumycetoma causative agents
Mucorales
Fusarium spp.
Candida tropicalis
Candida parapsilosis
Medium group
Scedosporium spp.
Lomentospora prolificans
Coccidioides spp.
Pichia kudriavzeveii (Candida krusei)
Cryptococcus gattii
Talaromyces marneffei
Pneumocystis jirovecii
Paracoccidioides spp.

Neden böyle bir sınıflama, sayılarla…

Pathogen	Final ranking of pathogens	Geographic distribution	Mortality
Critical priority group			
Cryptococcus neoformans	1	Global	41–61%
Candida auris	2	Global	29–53%
Aspergillus fumigatus	3	Global	47–88%
Candida albicans	4	Global	20–50%
High priority group			
Nakaseomyces glabrata (*Candida glabrata*)	5	Global	20–50%
Histoplasma spp.	6	Global	21–53% (HIV/AIDS patients) 9–11% (immunosuppressed patients)
Eumycetoma causative agents	7	Global	Lack of data. Thought to be low
Mucorales	8	Global	23–80% (adult patients) 72.7% (pediatric patients)
Fusarium spp.	9	Global	43–67%
Candida tropicalis	10	Global	55–60% (adult patients) 26–40% (pediatric patients)
Candida parapsilosis	11	Global	20–45%
Medium priority group			
Scedosporium spp.	12	Global	42–46%
Lomentospora prolificans	13	Global	50–71% (adult patients) 50% (immunocompromised children)
Coccidioides spp.	14	Americas	2–13%
Pichia kudriavzeveii (*Candida krusei*)	15	Global	44–67%
Cryptococcus gattii	16	Global	10–23% (CNS infections) 15–21% (pulmonary infections)
Talaromyces marneffei	17	South-East Asia, China	12–21%
Pneumocystis jirovecii	18	Global	0–100%

COVID-19 sürecinde fungal infeksiyonlar

- SARSCoV-2 ile yeni ortaya çıkmamıştır
- COVID-19 öncesi, influenza , parainfluenza ve RSV ile de birlikte bildirilmiştir.

- Pandemide, CAPA en sık (bilinen!) araştırılan ve tanımlanmış, bildirilen ilk İFİ olmasına rağmen, mayalara bağlı fungal koenfeksiyonlar ve aspergillus dışı küf infeksiyonları da sıklıkla raporlanmıştır.

- CAPA ile karşılaştırıldığında, daha nadir olarak küf patojenleri ile koenfeksiyon veya süperinfeksiyonlar bildirilmiş olsa da, gerçek sayısal değeri çok daha yüksek olabilir. Çünkü havadaki sayısız mantarın solunum yollarına kolay erişimi ve altta yatan şiddetli COVID-19 kaynaklı akciğer hasarı bu ajanlarla İFİ olasılığını artırmaktadır.

COVID-19 salgını, iklim değişikliği ve insan ve hayvan habitatındaki değişiklikler, antifungal ilaçlara karşı artan direnç ve artan sayıda bağışıklığı baskılanmış hasta, son zamanlarda patojenik mantar infeksiyonlarında küresel bir artışa neden oldu.

World Health Organization (WHO) Fungal Priority Pathogens List, 2022

Basilse K et al. J. Fungi 2022, 8, 58

COVID-19 öncesi elimizde olanlar…

Global guideline for the diagnosis and management of rare mould infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and the American Society for Microbiology

Ocak 2018-Temmuz 2020

Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium

Aralık 2017-Aralık 2018

AŞH yıllara göre…

	2019	2020	2021	2022	2023
Mucorales	0	1	2	3	0
Fusarium spp	0	0	1	2	1
Scedosporium spp	0	0	1	0	0
Cladosporium spp	0	0	0	1	1
Saprochaete capitata	0	0	1	0	0
Geotrichum candidum	0	0	1	0	0
Cryptoccus spp	0	1	1	2	0

Dr. Bedia Mert Dinç ve Dr Sema Turan'ın izniyle

MİÇG
TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ
MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Pandemi Sürecinde Aspergillus Türü Mantarlara Bağlı Akciğer İnfeksiyonları Dışındaki Küf Mantarlarına Bağlı İnfeksiyonlar: Çok merkezli Çalışma

Esra Kazak, Süda Tekin, Cağla Karakoc, İlkay Karaoğlan, Türkan Tüzün,

öre hasta ve etken dağılımı

	ETKEN						
Enfeksiyon Bölgesi	*Mucorales*	*Fusarium*	*Aspergillus*	*Alternaria*	*Sceidosporium*	*Penicillium*	*Pseudallescheria boydi*
İzole Orbital Enfeksiyon	1						
İzole Sinüs Enfeksiyonu			1 Covid-19				
Rinoorbital Enfeksiyon	42 (% 77.7) DM 28(% 51.8) Covid-19		5 Covid-19	3(3 beyin)		1	
Kafa tabanı Osteomiyelit					1		1
Beyin Apsesi			1 Covid-19				
Akciğer Enfeksiyonu	1	1 Covid-19			1 Covid-19	1 Covid-19	
Cilt Enfeksiyonu		1	1 Covid-19				
Cerrahi Alan Enfeksiyonu	1 Covid-19						
Kan Dolaşımı Enfeksiyonu		1 Covid-19	3 Covid-19				
Gastrointestinal tutulum	1						
TOPLAM SAYI	60	13	16	4	3	2	1

**Bazı hastalarda birden fazla etken ve/veya farklı enfeksiyon tabloları birarada izlenmiştir*

- Hastalarda Covid-19 hastalığı ve fungal enfeksiyon ile arasındaki süre 2-320 gün arasında değişmektedir
- İlk 30 gün içinde fungal enfeksiyon görülen 24 hastadan 17'si rinoserebral mukormikoz ile takip edilmiştir
- Ondört hastaya 1-3 ay, 3 hastaya 3-6 ay, 2 hasta 6 aydan uzun süre sonra fungal enfeksiyon tanısı konulmuştur

Dr Esra Kazak'ın izniyle

Received: 24 October 2022 | Revised: 13 February 2023 | Accepted: 15 February 2023
DOI: 10.1111/myc.13579

ORIGINAL ARTICLE

mycoses WILEY

Secondary invasive fungal infection in hospitalised patients with COVID-19 in the United States

Abstract

Background: Invasive fungal infections (IFIs) have been identified as a complication in patients with Coronavirus disease 2019 (COVID-19). To date, there are few US studies examining the excess humanistic and economic burden of IFIs on hospitalised COVID-19 patients.

Objectives: This study investigated the incidence, risk factors, clinical and economic burden of IFIs in patients hospitalised with COVID-19 in the United States.

Patients/Methods: Data from adult patients hospitalised with COVID-19 during 01 April 2020–31 March 2021 were extracted retrospectively from the Premier Healthcare Database. IFI was defined either by diagnosis or microbiology findings plus systemic antifungal use. Disease burden attributable to IFI was estimated using time-dependent propensity score matching.

Results: Overall, 515,391 COVID-19 patients were included (male 51.7%, median age: 66 years); IFI incidence was 0.35/1000 patient-days. Most patients did not have traditional host factors for IFI such as hematologic malignancies; COVID-19 treatments including mechanical ventilation and systemic corticosteroid use were identified as risk factors. Excess mortality attributable to IFI was estimated at 18.4%, and attributable excess hospital costs were $16,100.

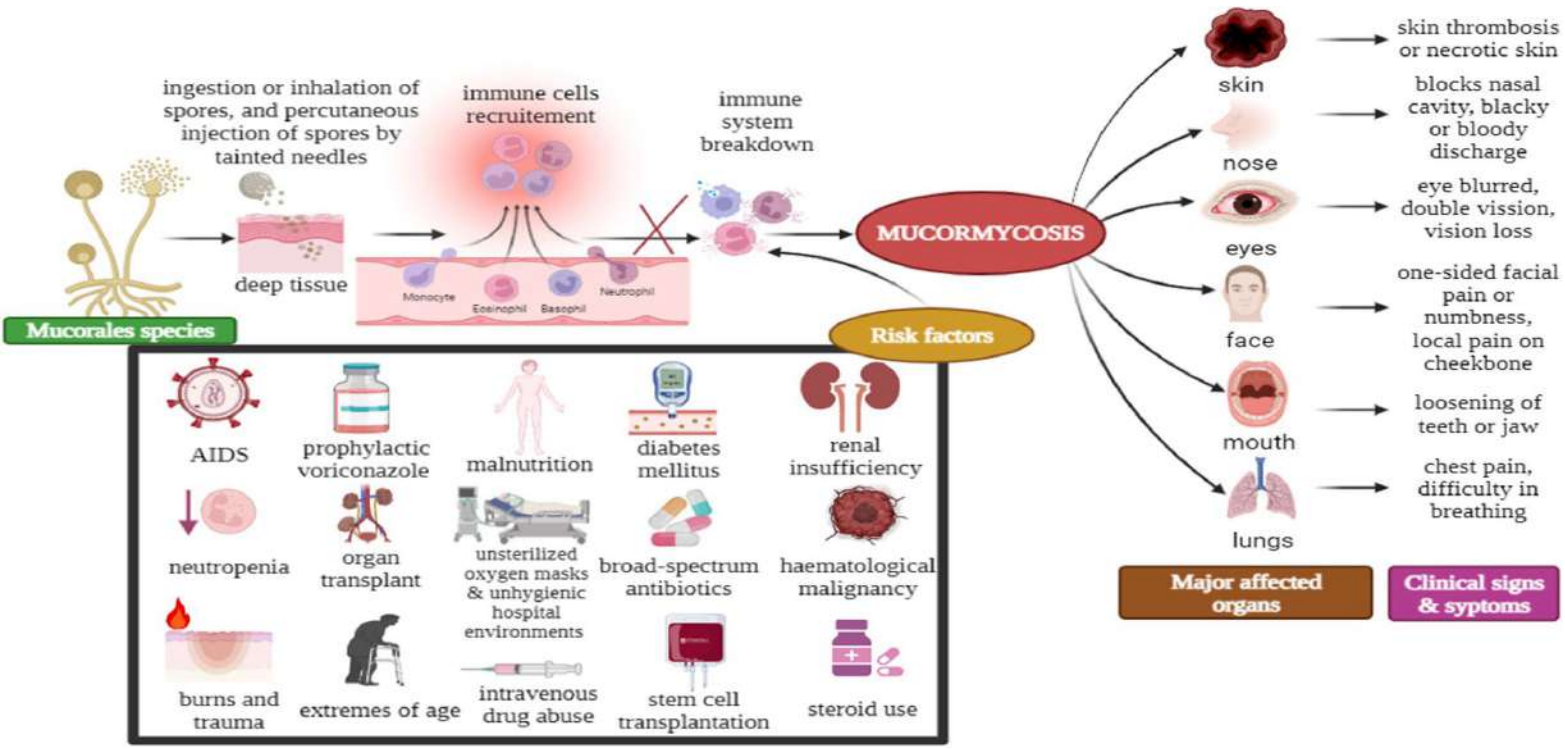
Conclusions: Invasive fungal infection incidence was lower than previously reported, possibly due to a conservative definition of IFI. Typical COVID-19 treatments were among the risk factors identified. Furthermore, diagnosis of IFIs in COVID-19 patients may be complicated because of the several non-specific shared symptoms, leading to underestimation of the true incidence rate. The healthcare burden of IFIs was significant among COVID-19 patients, including higher mortality and greater cost.

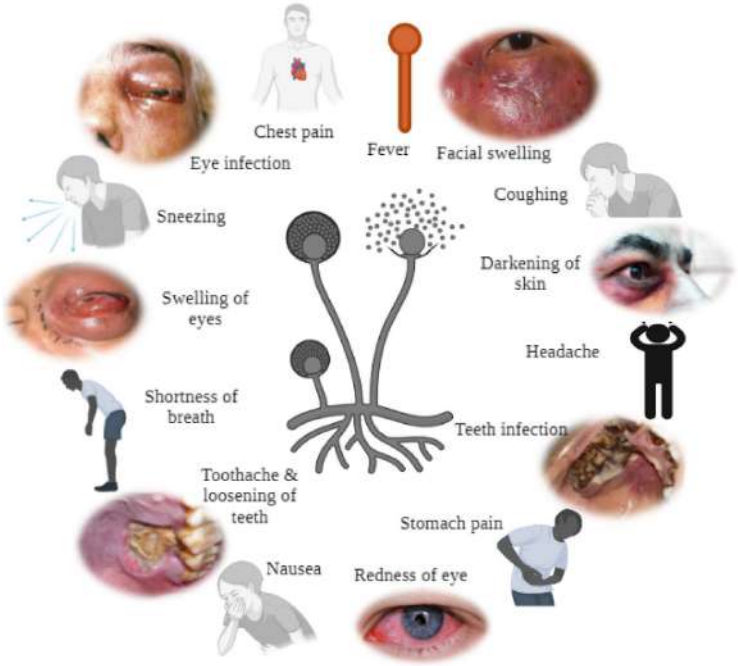
- Hastaların çoğunda İFİ için bilinen risk faktörleri YOK
- MV ve YBU ihtiyacı RİSK faktörü
- COVID-19 hastalarında İFİ tanısı, ortak SSx ve görüntüleme bulguları nedeniyle komplike
- Gerçek insidansı???

	n	% (95% CI)	Incidence/1000 patient-days (95% CI)
Main cohort, total incidence	1442	0.28 (0.27–0.29)	0.35 (0.33–0.36)
Invasive candidiasis	642	0.12 (0.11–0.13)	0.15 (0.14–0.17)
Invasive aspergillosis	262	0.05 (0.04–0.06)	0.06 (0.06–0.07)
Other IFI	561	0.11 (0.10–0.12)	0.13 (0.12–0.15)
Coccidioidomycosis	15	0 (0.00–0.00)	0 (0.00–0.01)
Histoplasmosis	2	0 (0.00–0.00)	0 (0.00–0.00)
Blastomycosis	1	0 (0.00–0.00)	0 (0.00–0.00)
Cryptococcosis	33	0.01 (0.00–0.01)	0.01 (0.00–0.01)
Mucormycosis	2	0 (0.00–0.00)	0 (0.00–0.00)
Pneumocystis	12	0 (0.00–0.00)	0 (0.00–0.01)
Other specified mycoses[a]	266	0.05 (0.05–0.06)	0.06 (0.06–0.07)
Unspecified mycosis[b]	341	0.07 (0.06–0.07)	0.08 (0.07–0.09)
ICU subgroup, total incidence	1248	0.87 (0.82–0.92)	0.76 (0.72–0.80)
Invasive candidiasis	564	0.39 (0.36–0.43)	0.34 (0.31–0.37)
Invasive aspergillosis	222	0.16 (0.13–0.18)	0.13 (0.12–0.15)
Other IFI	483	0.34 (0.31–0.37)	0.29 (0.27–0.32)
Coccidioidomycosis	9	0.01 (0.00–0.01)	0.01 (0.00–0.01)
Histoplasmosis	2	0 (0.00–0.00)	0 (0.00–0.00)
Blastomycosis	1	0 (0.00–0.00)	0 (0.00–0.00)
Cryptococcosis	28	0.02 (0.01–0.03)	0.02 (0.00–0.02)
Mucormycosis	2	0 (0.00–0.00)	0 (0.00–0.00)
Pneumocystis	10	0.01 (0.00–0.01)	0.01 (0.00–0.01)
Other specified mycoses[a]	232	0.16 (0.14–0.18)	0.14 (0.12–0.16)
Unspecified mycosis[b]	298	0.21 (0.18–0.23)	0.18 (0.16–0.20)

Mukormikoz

- Çoğunlukla immukompromize hastalarda hızlı ilerleyen infeksiyonlara, yaşamı zorlaştıran morbidite ve mortaliteye neden
- Risk faktörleri arasında diabetes mellitus, hematolojik maligniteler, solid organ transplantasyonu, aşırı demir yüklenmesi, nötropeni ve uzun süreli glukokortikoid kullanımı, immunsüpresyon





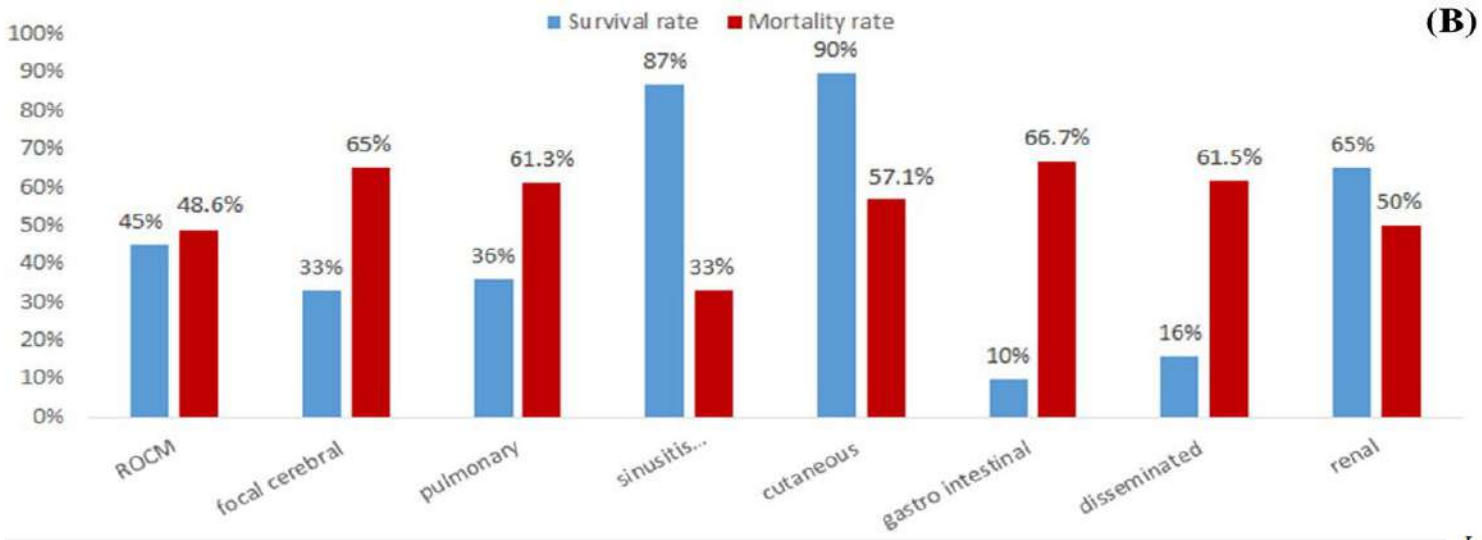
L. Özbek et al. / Clinical Microbiology and Infection 29 (2023) 722–731

Molecular Biology Reports (2022) 49:4977–4988

Mukormikoz

Hemen adjuvan cerrahi ve antifungal başlanması gereken tıbbi acil!!

Form of Mucormycosis	Part of the body mostly affected	Type of population commonly seen in	Symptoms
Rhino-orbito-cerebral	Brain	Uncontrolled diabetes, kidney transplant patients	Fever, one-sided facial swelling, headache, nasal or sinus congestion, black lesions on nasal bridge or upper inside of mouth that quickly become more severe
Pulmonary Mucormycosis	Lungs	Cancer, organ transplant or stem cell transplant patients	Fever, cough, chest pain, shortness of breath
Gastrointestinal Mucormycosis	Stomach, colon and intestine	Young children, especially premature infants less than 1 month of age, who have had medications, surgery	Abdominal pain, nausea and vomiting, gastrointestinal bleeding
Cutaneous Mucormycosis	Damaged skin such as cuts, burns, wounds or other type of skin trauma	both immunocompetent and immunocompromised individuals with higher prevalence in immunocompetent individuals	Darkened skin, blisters or ulcers, pain, warmth, excessive redness, or swelling around a wound
Disseminated Mucormycosis	Brain, spleen, heart, and skin	Immunocompromised patients	Fever, chills, green, mucopurulent sputum



Global epidemiyoloji ve prevelans

Molecular Biology Reports (2022) 49:4977–4988

L. Özbek et al. / Clinical Microbiology and Infection 29 (2023) 722–731

COVID-19 ile ilişkili mukormikoz (CAM)

- Aspergillus dışı en yaygın bildirilen küf enfeksiyonu
- Çoğu erken vaka Hindistan'da ikinci dalgada; 2021 başları, pandemide epidemi
- Orta Doğu, Avustralya, Asya, Avrupa, Güney Amerika ve ABD'den de bildirimler
- Hindistan'da vakaların kümelenmesi konusunda çok fazla spekülasyon yapılmıştır.

  -Hindistan'ın büyük diyabetik nüfusu,

  - tropikal ve subtropikal nemli iklim gibi çevresel faktörler,

  - Mucorales sporlarının varlığı ve

  -kortikosteroid kullanımında uygulama varyasyonları salgın ile İlişkilendirilmekte

Current Fungal Infection Reports (2022) 16:87–97
Nature Micro biology | VOL 7 | August 2022 | 1127–1140

	COVID-19-associated mucormycosis (n=80)*	Rhino-orbital cerebral disease (n=59)	Pulmonary disease† (n=20)
Median age (range), years	55 (10-86)	54 (10-79)	57 (23-86)
Male-to-female-patient ratio	62:18 (78%:23%)	43:16 (73%:27%)	18:2 (90%:10%)
Country of case origin	India (42 [53%]), USA (8 [10%]), Pakistan (5 [6%]), France (4 [5%]), Mexico (4 [5%]), Iran (4 [5%]), Russia (2 [3%]), Austria (1 [1%]), Bangladesh (1 [1%]), Brazil (1 [1%]), Chile (1 [1%]), Czech Republic (1 [1%]), Germany (1 [1%]), Italy (1 [1%]), Kuwait (1 [1%]), Lebanon (1 [1%]), Turkey (1 [1%]), UK (1 [1%])	India (41 [69%]), USA (4 [7%]), Pakistan (1 [2%]), France (2 [3%]), Mexico (3 [5%]), Iran (4 [7%]), Russia (2 [3%]), Bangladesh (1 [2%]), Turkey (1 [2%])	India (1 [5%]), USA (4 [20%]), Pakistan (4 [20%]), France (2 [10%]), Mexico (1 [5%]), Austria (1 [5%]), Chile (1 [5%]), Czech Republic (1 [5%]), Germany (1 [5%]), Italy (1 [5%]), Kuwait (1 [5%]), Lebanon (1 [5%]), UK (1 [5%])
Underlying conditions	Diabetes (66 [83%]; 55 [83%] of which had uncontrolled diabetes), haematological malignancy (5 [6%]), lymphopenia (2 [3%]), hypertension (1 [1%]), chronic kidney disease (1 [1%]), severe obesity (1 [1%]), no known risk factor (4 [5%])	Diabetes (55 [93%]; 48 [87%] of which had uncontrolled diabetes), haematological malignancy (1 [2%]), hypertension (1 [2%]), no known risk factor (2 [3%])	Diabetes (11 [55%]; 7 [64%] of which had uncontrolled diabetes), haematological malignancy (4 [20%]), lymphopenia (1 [5%]), chronic kidney disease (1 [5%]), severe obesity (1 [5%]), no known risk factor (2 [10%])
Comorbidities‡	Hypertension (14 [18%]), kidney disease (6 [8%]), obesity (3 [4%]), cardiac disease (5 [6%]), asthma (2 [3%]), hyperlipidaemia (2 [3%])	Hypertension (7 [12%]), kidney disease (4 [7%]), obesity (1 [2%]), cardiac disease (2 [3%]), asthma (2 [3%]), hyperlipidaemia (2 [3%])	Hypertension (6 [30%]), kidney disease (2 [10%]), cardiac disease (3 [15%]), hypothyroidism (1 [5%]), pancreatitis (1 [5%]), obesity (1 [5%])
COVID-19 diagnosis	On admission (58 [68%]), previous (10 [13%]), during admission (1 [1%]), unknown (14 [18%])	On admission (37 [63%]), previous (9 [15%]), unknown (13 [22%])	On admission (17 [85%]), previous (1 [5%]), during admission (1 [5%]), unknown (1 [5%])
COVID-19 severity	Severe or critical (36 [45%]), mild or moderate (36 [45%]), asymptomatic (2 [3%]), unknown (6 [8%])	Severe or critical (19 [32%]), mild or moderate (33 [56%]), asymptomatic (2 [3%]), unknown (5 [8%])	Severe or critical (16 [80%]), mild or moderate (4 [20%])
Intensive care unit admission	Yes (38 [48%]), no (34 [43%]), unknown (8 [10%])	Yes (19 [32%]), no (33 [56%]), unknown (7 [12%])	Yes (18 [90%]), no (1 [5%]), unknown (1 [5%])
Corticosteroids administered	Yes (63 [79%])§, no (14 [18%]), unknown (3 [4%])	Yes (47 [80%]), no (10 [17%]), unknown (2 [3%])	Yes (15 [75%]), no (4 [20%]), unknown (1 [5%])
Causative Mucorales spp	Rhizopus spp (16 [20%]), Mucor spp (6 [8%])**, R arrhizus (11 [14%]), R microsporus (7 [9%]), Lichtheimia spp (1 [1%]), Rhizomucor pusillus (1 [1%]), not specified (39 [49%])	Rhizopus spp (10 [17%]), Mucor spp (6 [10%])**, R arrhizus (8 [14%]), Lichtheimia spp (1 [2%]), R microsporus (1 [2%]), not specified (34 [58%])	Rhizopus spp (6 [30%]), R microsporus (6 [30%]), R arrhizus (3 [15%]), R pusillus (1 [5%]), not specified (4 [20%])
Antifungal therapy	Liposomal amphotericin B (54 [68%]), conventional amphotericin B (9 [11%]), unknown amphotericin B formulation (7 [9%]), amphotericin lipid complex (2 [3%]), voriconazole (5 [6%]), isavuconazole (5 [6%]), posaconazole (6 [8%]), caspofungin (2 [3%]), micafungin (1 [1%]), antifungal combination (ie, drugs simultaneously; 14 [18%]), none (2 [3%]), unknown (1 [1%])	Liposomal amphotericin B (44 [75%]), conventional amphotericin B (5 [8%]), unknown amphotericin B formulation (6 [10%]), amphotericin lipid complex (2 [3%]), voriconazole (2 [3%]), isavuconazole (2 [3%]), posaconazole (6 [10%]), caspofungin (1 [2%]), antifungal combination (ie, drugs simultaneously; 10 [17%]), none (1 [2%]), unknown (1 [2%])	Liposomal amphotericin B (10 [50%]), conventional amphotericin B (4 [20%]), unknown amphotericin B formulation (1 [5%]), voriconazole (3 [15%]), isavuconazole (3 [15%]), caspofungin (1 [5%]), micafungin (1 [5%]), antifungal combination (ie, drugs simultaneously; 4 [20%]), none (1 [5%])
Surgical intervention	Yes (45 [56%]), no (29 [36%]), deferred or unknown (6 [8%])	Yes (43 [73%]), no (12 [20%]), deferred or unknown (4 [7%])	Yes (2 [10%]), no (16 [80%]), deferred or unknown (2 [10%])
Therapeutic strategy	Systemic antifungals plus surgery (44 [55%]), systemic antifungals only (32 [40%]), surgery only (1 [1%]), none (2 [3%]), unknown (1 [1%])	Systemic antifungals plus surgery (42 [71%]), systemic antifungals only (15 [25%]), surgery only (1 [2%]), unknown (1 [2%])	Systemic antifungals plus surgery (2 [10%]), systemic antifungals only (17 [85%]), none (1 [5%])
Fungal coinfections	Aspergillosis (9 [11%]), none (71 [89%])	Aspergillosis (3 [5%]), none (56 [95%])	Aspergillosis (6 [30%]), none (14 [70%])
Outcome	Survived (37 [46%]), died (39 [49%]), unknown (4 [5%])	Survived (33 [56%]), died (22 [37%]), unknown (4 [7%])	Survived (4 [20%]), died (16 [80%])
Life-changing morbidities in survivors	Loss of vision (19 [24%])	Loss of vision (19 [32%])	-

- 18 Ülke, 80 olgu

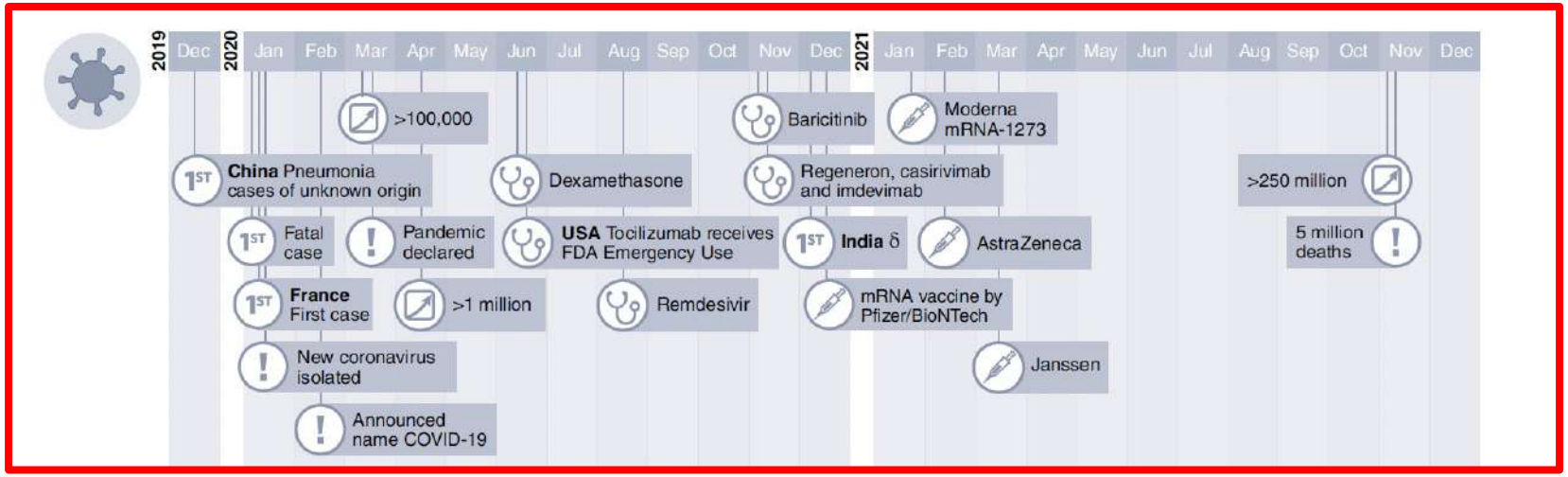
42 Hindistan, 8 ABD

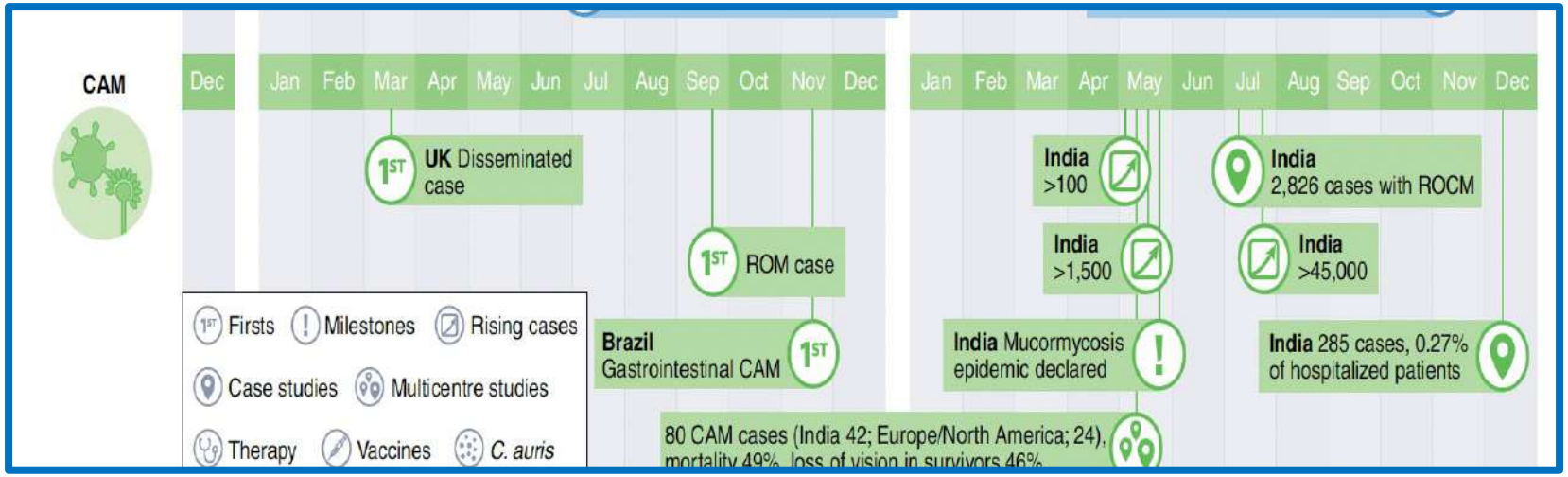
5 Pakistan, 4 Fransa, İran..

- % 8 Daha önce Covid-19

% 93 Tanı anında Covid-19

- YBÜ takipli Covid-19 hastalarında % 0.3-0.8
- % 95 Altta yatan risk faktörü; HT 2. sıklıkta
- %79 steroid +
- Rhizopus spp
- CAPA birlikteliği!!!!!


2019
Dec
2020
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec
2021
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec
>100,000
China Pneumonia cases of unknown origin
Fatal case
Pandemic declared
France First case
>1 million
New coronavirus isolated
Announced name COVID-19
Dexamethasone
USA Tocilizumab receives FDA Emergency Use
Remdesivir
Baricitinib
Regeneron, casirivimab and imdevimab
India δ
mRNA vaccine by Pfizer/BioNTech
Moderna mRNA-1273
AstraZeneca
Janssen
>250 million
5 million deaths


CAM
Dec
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec
UK Disseminated case
ROM case
Brazil Gastrointestinal CAM
India >100
India >1,500
India Mucormycosis epidemic declared
India 2,826 cases with ROCM
India >45,000
India 285 cases, 0.27% of hospitalized patients
80 CAM cases (India 42; Europe/North America; 24),
Firsts
Milestones
Rising cases
Case studies
Multicentre studies
Therapy
Vaccines
C. auris

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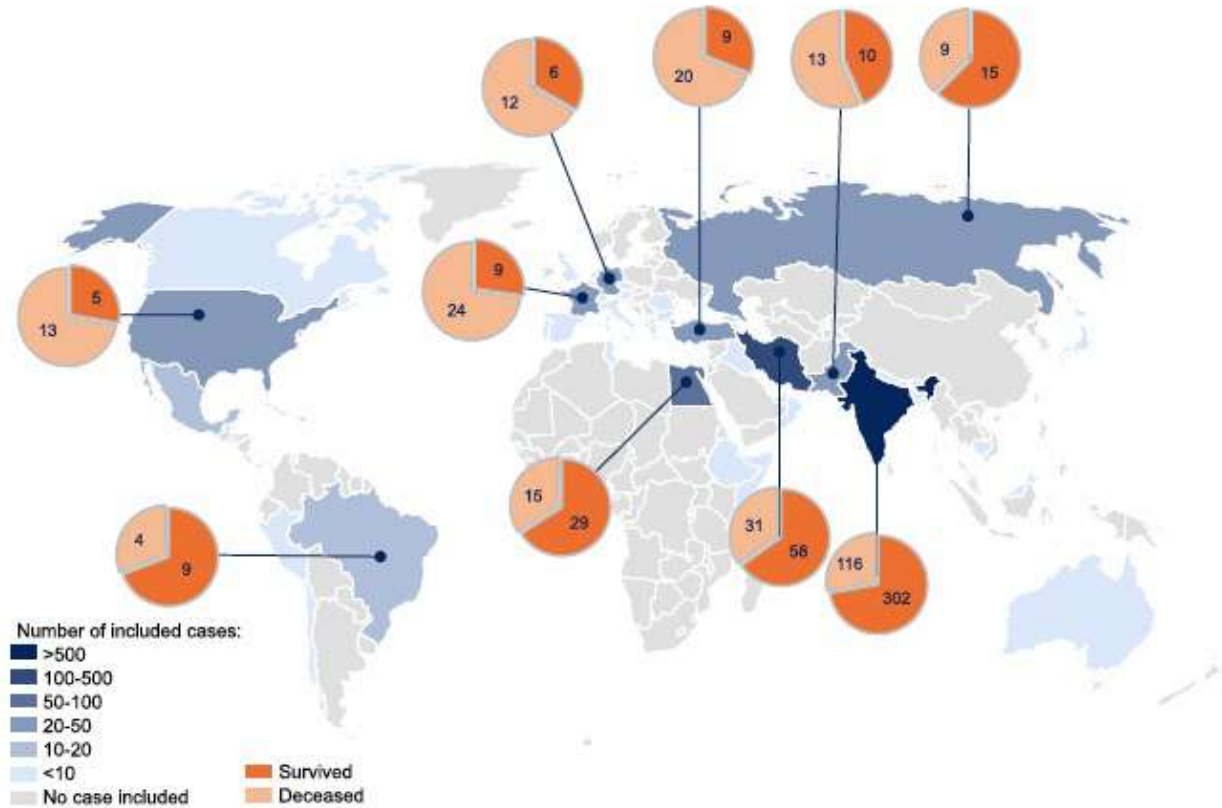
Systematic review

COVID-19—associated mucormycosis: a systematic review and meta-analysis of 958 cases

Laşin Özbek [1], Umur Topçu [1], Mehtap Manay [1], Buğra Han Esen [1], Sevval Nur Bektas [1], Serhat Aydın [1], Barış Özdemir [1], Sofya N. Khostelidi [2], Nikolai Klimko [2], Oliver Cornely [3], Johnny Zakhour [4], Souha S. Kanj [4], Danila Seidel [3], Martin Hoenigl [5], Önder Ergönül [6, 7, *]



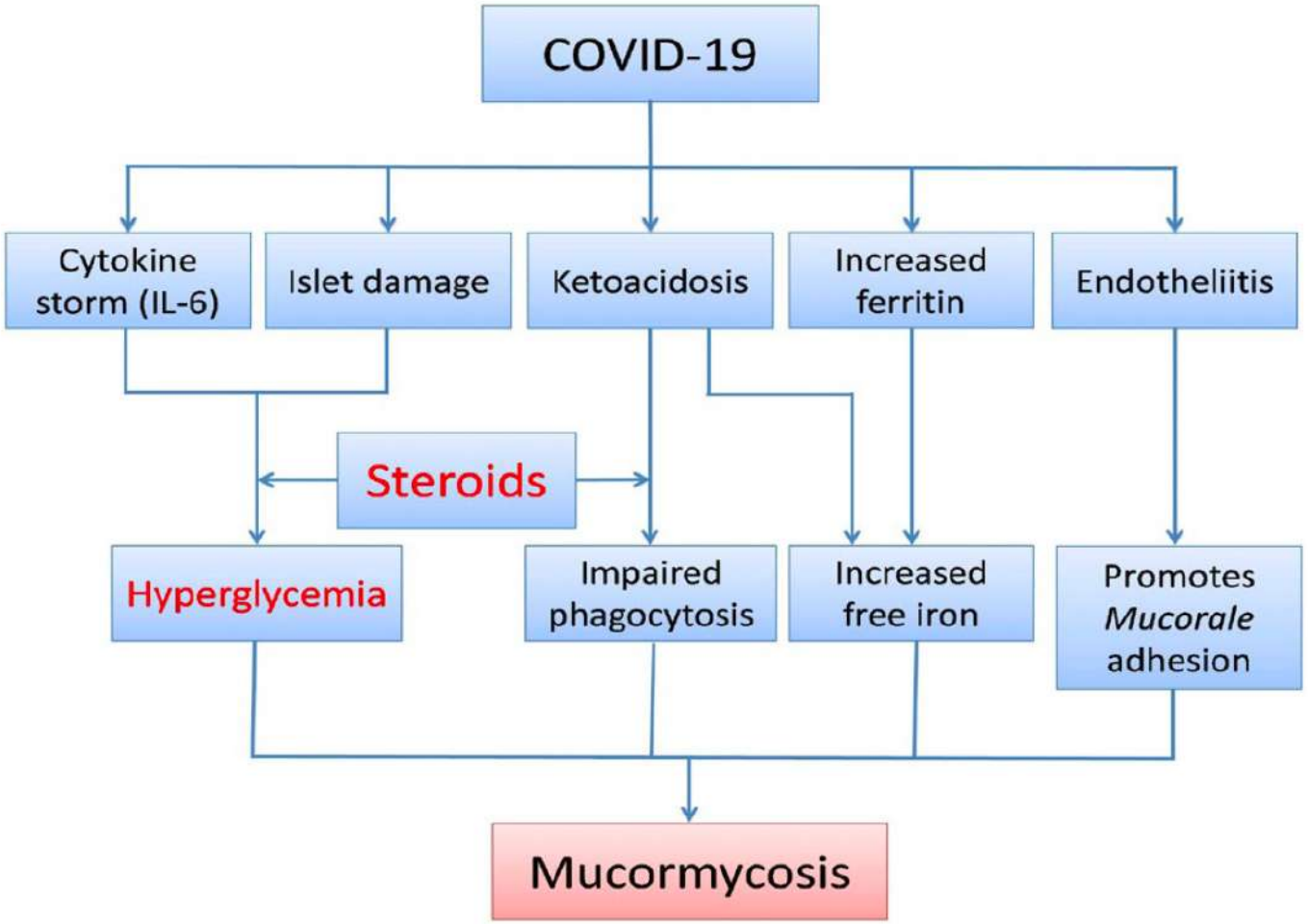
CAM Risk Faktörleri

- Kontrolsüz diyabet ve hiperglisemi için temel risk faktörleri.

- Olguların % 83-94'ünde diyabet (+); %67-83'ü DM’in kötü kontrol edildiği gösterildi.

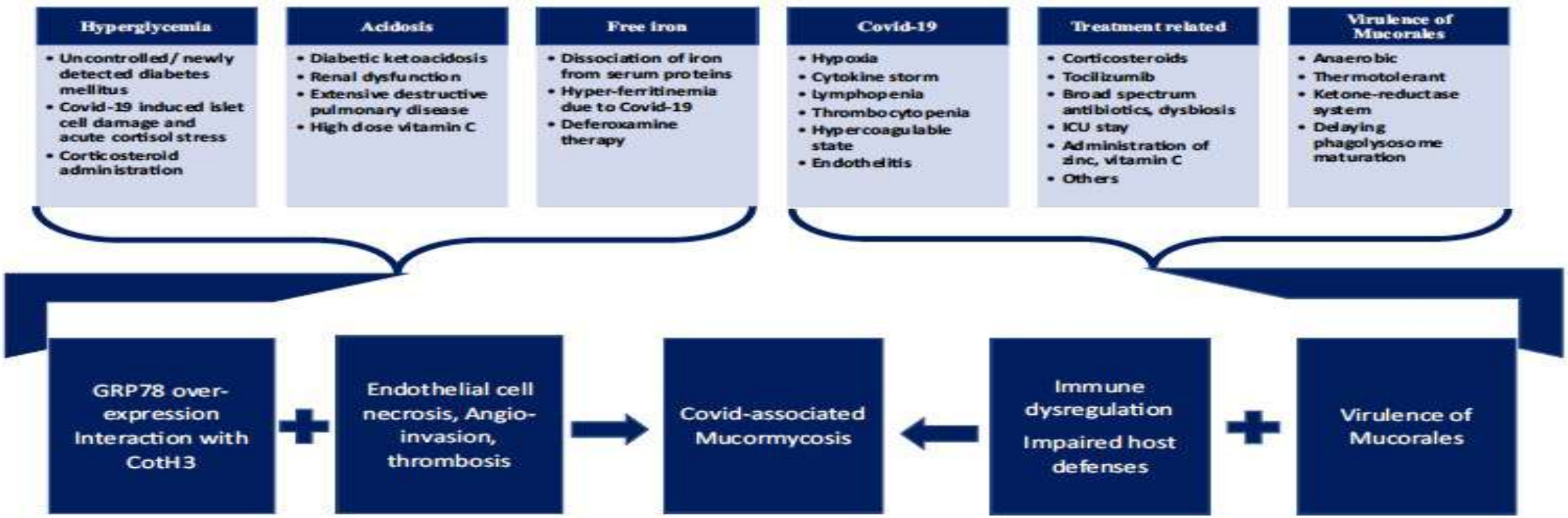
- CAM için diğer risk faktörleri arasında COVID-19 öncesi dönemde olduğu gibi, hematolojik malignite, organ ve hematopoietik kök hücre nakli, son dönem böbrek hastalığı ve travma da yer almaktadır.

Current Fungal Infection Reports (2022) 16:87–97

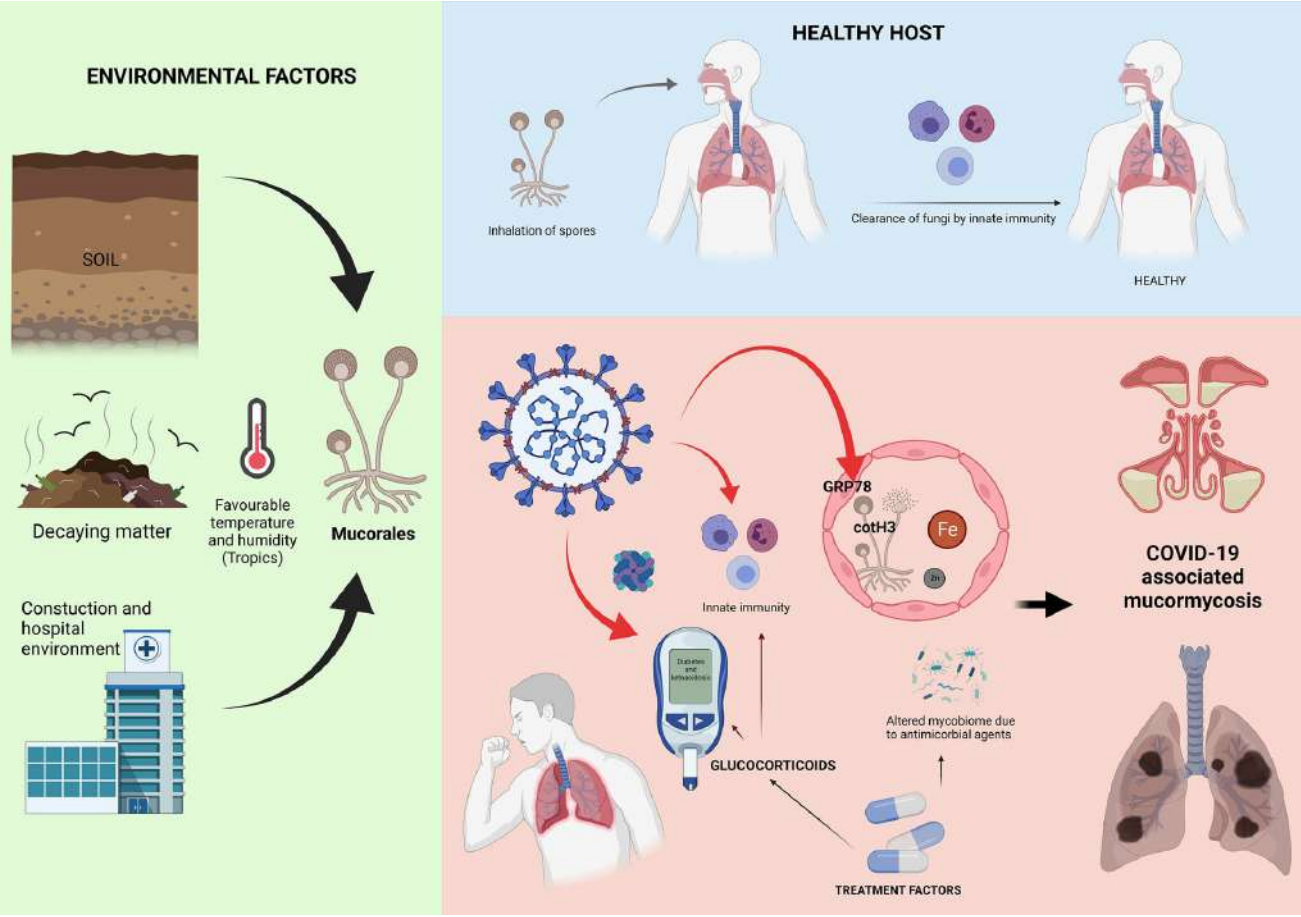


- Diyabet ve steroidlere bağlı oluşan hiperglisemi küf gelişimine destek
- Diyabetik ketoasidoz (DKA) gibi asidemik durumlar, bağlanmamış demiri artırır ve küflerin büyümesini destekler
- DKA'nın yan ürünleri (B-hidroksibutirat, glukoz ve demir) Rhizopus'un epitelyuma girdiği reseptör olan GRP78'in ve GRP78'i bağlayan mantar proteini CotH'un her iki hücre ekspresyonunu da arttırır

Mycoses. 2021;64:1452–1459


Hyperglycemia
• Uncontrolled / newly detected diabetes mellitus
• Covid-19 induced islet cell damage and acute cortisol stress
• Corticosteroid administration
Acidosis
• Diabetic ketoacidosis
• Renal dysfunction
• Extensive destructive pulmonary disease
• High dose vitamin C
Free iron
• Dissociation of iron from serum proteins
• Hyper-ferritinemia due to Covid-19
• Deferoxamine therapy
Covid-19
• Hypoxia
• Cytokine storm
• Lymphopenia
• Thrombocytopenia
• Hypercoagulable state
• Endothelitis
Treatment related
• Corticosteroids
• Tocilizumib
• Broad spectrum antibiotics, dysbiosis
• ICU stay
• Administration of zinc, vitamin C
• Others
Virulence of Mucorales
• Anaerobic
• Thermotolerant
• Ketone-reductase system
• Delaying phagolysosome maturation
GRP78 over-expression Interaction with CotH3
Endothelial cell necrosis, Angio-invasion, thrombosis
Covid-associated Mucormycosis
Immune dysregulation
Impaired host defenses
Virulence of Mucorales

CAM patofizyoloji



İnsan endotel hücreleri üzerindeki 78 kDa proteini (GRP78), Mucorales tarafından vasküler invazyon için temel reseptör proteini (CotH3) etkileşir. Hiperglisemi, diyabetik ketoasidoz, ve demirin varlığı bu etkileşimi destekler ve mantarların çoğalması için elverişli ortam.

SARS-CoV-2 ayrıca doğrudan da GRP78'in ekspresyonunu artırır, diyabetik ketoasidozu hızlandırabilir ve doğal bağışık hücre fonksiyonlarını etkiler. Ayrıca kullanılan glukokortikoidler COVID-19 tedavisi hiperglisemiye neden olur ve bağışıklığın baskılanması katkıda bulunur.

Parameter	Pre-COVID mucormycosis		COVID-associated mucormycosis		
Authors	Patel et al. 2020 [11••] $n=465$ (India)	Jeong et al. (2019) [10] $n=851$ (31% Asia)	Patel et al. (2021) [19••] $n=187$ (India)	Hoenigl et al. (2022) [24••] $n=80$ (53% India)	Watanabe et al. (2022) [33] $n=2312$ (88.67% India)
Type of study	Multi-center study	Systematic review and meta-analysis	Multi-center study	Review of cases from 18 countries	Systematic review and meta-analysis
Study period	1 January 2016–30 September 2017	January 2000–January 2017	1 September 2020–1 December 2020	1 October 2019–12 April 2021	Till 20 January 2022
Age in years	48	51	56.9	55	36–63
Male gender (%)	69.5	63	80.2	78	20–100
Pre-existing disease (%)					
DM (DKA in % of DM patients)	73.5 (14.6)	40 (21; status unknown in 248/851)	60.4 (8.6)	83 (49: available in 55/66)	82 (2.71)
Malignancy	09	32	1.1	06	2.6
Transplantation	7.7	14	1.6	-	-
Chronic kidney disease	20		-	06	15
Trauma	6.9	20	1.6	-	-
Others	0.6	03	2.7	19	-
No predisposing disease	11.8	18	32.6 (COVID-19 only)	05 (COVID-19 only)	-
Site of involvement (%)					
ROM (ROCM)	67.7 (32.7)	34 (9)	86.1 (27.33)	74 (37)	97 (25)
Pulmonary	13.3	20	8.6	25 (includes 15% disseminated)	2.7
Cutaneous	10.5	22	2.7	-	<1
GIT	2.6	8.5		<1	
Disseminated	2.8	13	2.1	-	
Others	03	03	0.5		
Corticosteroid administration (%)	3.7	-	78.7	79	77
Mortality (%)	52	46	44	49	29

- EN SIK MORTALİTE ile ilişkili komorbiditeler; DM , HT , malignensi, KBH, Pulmoner hast, kardiovask hastalık

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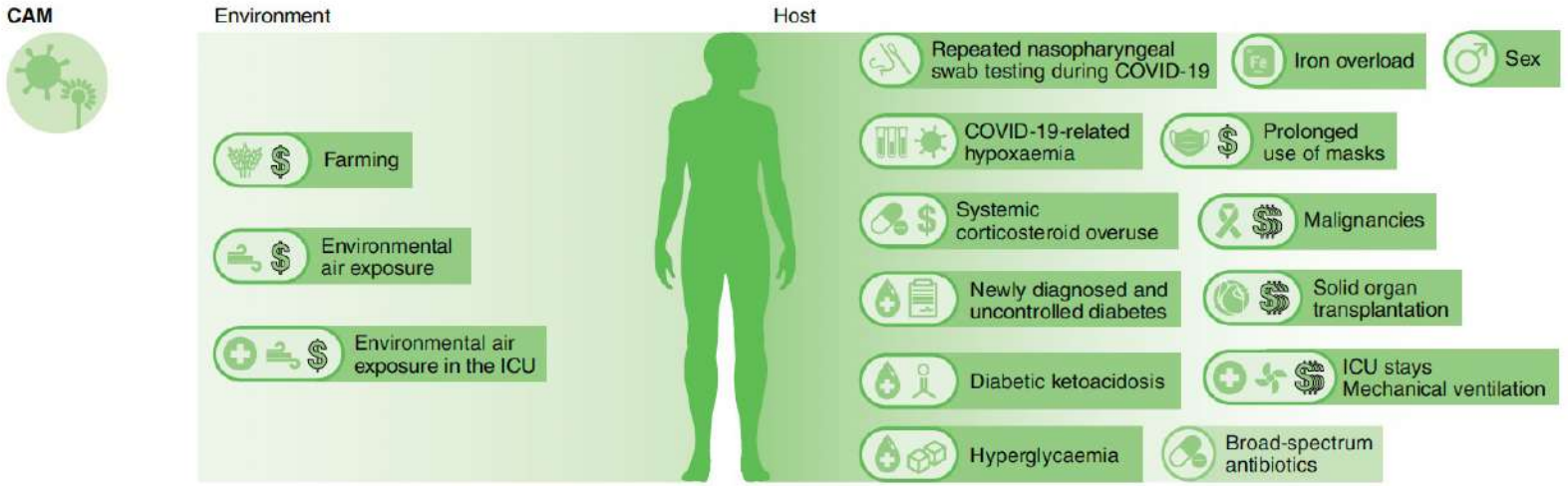
Current Fungal Infection Reports (2022) 16:206–220

CAM için risk faktörleri



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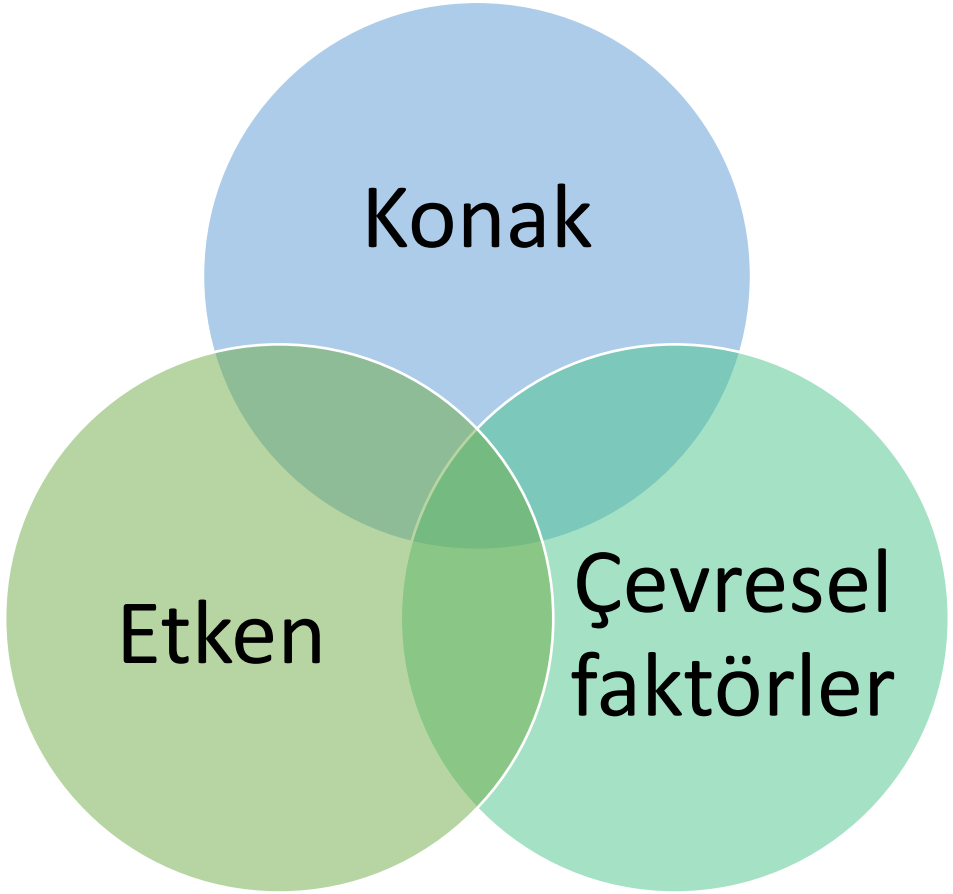
CAM

- Çoğu CAM vakası rinoserebrorbital,
- Pulmoner, kutanöz, dissemine ve gastrointestinal tutulumlar da bildirilmektedir.
- Genellikle COVID-19 tanısından sonraki 2 hafta
- CAM tanısı zordur ve yüksek şüphe ile tanıya gidilir. Neredeyse tüm CAM olgularında bx ile histopatoloji veya RT-PCR ile tanı
- Olguların %30 kadarında ayrıca CAPA mevcut.
- CAM **tedavisi** mukormikoz için kılavuzlar **önceden belirlenmiş olandan farklı değil!!!**
- CAM hastalarının tedavisinde sistemik antifungal (en yaygın olarak amfoterisinB) tedavi gerekir.
- Sıklıkla %78'i cerrahi debridman gerektirir
- Pulmoner CAM ile ölüm oranı %37 ila %80 arasında değişir; kötü prognoz göstergesi.

Current Fungal Infection Reports (2022) 16:87–97

Mukormikozda Epidemiyolojik Triad



Ortaya çıkan yeni durumu açıklamakta pratik bir yol

Epidemiyolojik triad- Çevresel faktörler

- Ne Biliyoruz

*Mukorel takımına ait, toprakta ve çürüyen materyallerde bulunur.

*İmmünkompromize opp.inf

*SBİ hastane kaynaklı salgınlar

*İnşaat ve havalandırma kaynaklı rinoorbital ve pulmoner

*Hindistan DM prevelansı en yüksek 2. ülke;

Salgın öncesi invaziv mukormikoz da en sık Hindistan ve Pakistan'da, erkeklerde yaygın

- Ne araştırılmalı
- Hindistan'ın batısı ile doğusu arasında fark?? İnşaat alanları??
- Hindistan dışı ülkelerdeki durum

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Epidemiyolojik triad- Etken

- Ne Biliyoruz

*Mukorel order, 261 tür ve 55 cins en az 38'i insanlada inf etkeni.

- *Rhizopus arhizus (Mucor, Rhizomucor, Lichtheimia, Apophysomyces, Saksenaea, Cunninghamella,)*
- Sporongiosporların sıklıkla inhalasyon, deriden inokülasyon nadiren oral yolla alınır

- Ne araştırılmalı

*Mukor etkenleri Kriptokokdaki gibi bir hipervirulans özelliği kazandı mı?

*SARS CoV2 immunmodülatör bir virüs mü?

*Tür spesifik farklılıklar ve konak immün sistem üzerideki etkileri

Konak Faktörleri ve SARS-CoV-2 ile ilişkisi

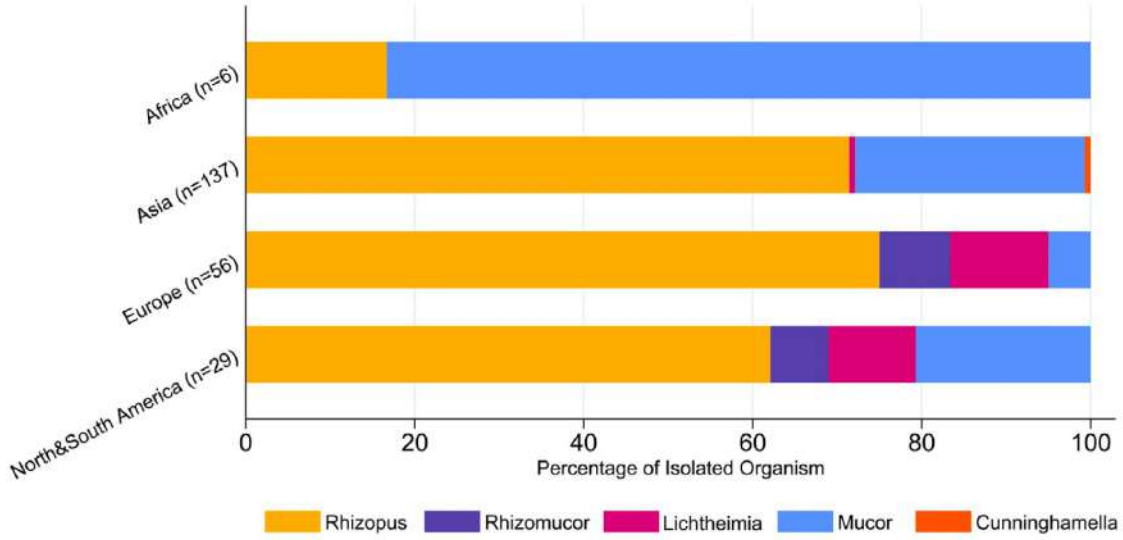
- İFİ için konvansiyonel risk faktörleri; *nötropeni, hematolojik maligniteler, SOT, hematopoietik kök hücre nakli, immünosupresif tedaviler (T-hücrelerini hedef) (kalsinörin inhibitörleri, tümör nekrozu faktör inhibitörleri, lenfosit spesifik monoklonal antikorlar, belirli bir dozda uzun süreli kortikosteroid kullanımı 0,3 mg/kg [son iki ayda 3 hafta), ve bazı kalıtsal immün yetmezlik hastalıkları*
- *SARS-CoV-2 ve DM, Ferritin ve Glukokortikoid ilişkisi ile Mukormikoz bağlantısı*

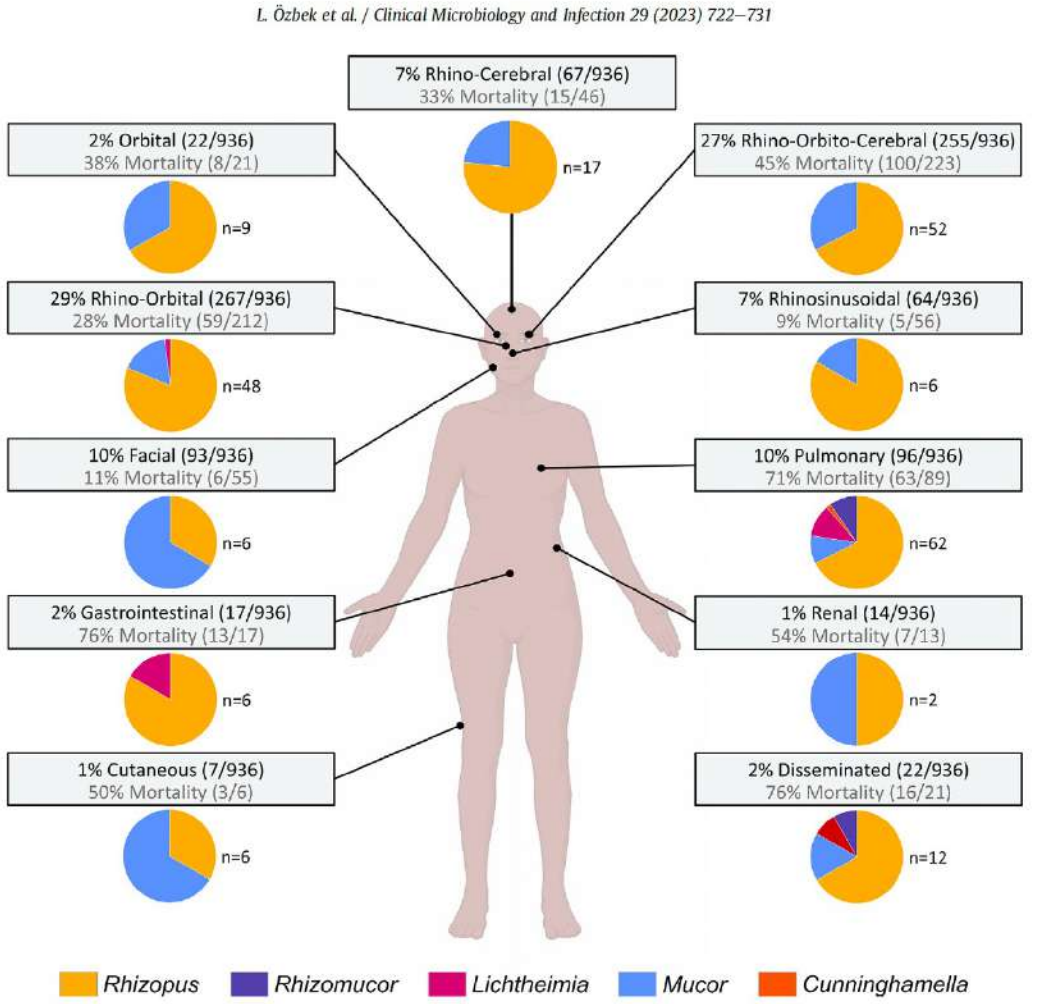
- COVİD-19 hastalarında yüksek düzey *GRP78* ve fungal yüzeylerdeki *CotH3* ile etkileşimi
- SARS-CoV-2 ‘nin neden olduğu endotel disfonk ve mukor giriş yolu?
- COVİD-19 için kullanılan tedavi ve mukor üzerine etkileri

CAM’da en ler…

- DM en sık risk faktörü
- En sık Hindistan’da
- Rinoserebraorbital(RSO) form en sık
- Hindistan dışı olgularda DM yanısıra HT ve KBH en sık risk
- Olguların çoğunda sistemik steroid kullanımı
- Pulmoner CAM olgularının çoğu YBÜ ve ağır COVID-19
- RSO formlarda COVID-19, pulmoner, dissemine ve GIS formları göre daha hafif seyir
- *Rhizopus spp* en sık
- Tedavide en sık LAMB (*Mukormikozun üç önemli tedavi prensibi, altta yatan hastalığın veya risk faktörünün kontrolü, nekrotik enfekte dokunun cerrahi debridmanı ve spesifik antifungal tedavidir.*)

Etken Dağılımı ve Mortalite





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Mukormikozda fatalite belirleyicileri

- Prepandemik döneme göre daha ileri yaş
- Pandemi öncesine göre; DM , malignansi ve diğer immkompromize durumlar majör risk
- Kutanöz form etkenleri prepandemik dönemde daha fazla
- Pulmoner CAM insidansı pandemide daha az bulunmuş
- Aspergillus koinf prepandemik döneme göre daha yüksek (%9)

	Univariate analysis		
Variable	Odds ratio	95% Confidence interval	p
Age >65 y	2.032	1.445–2.859	<0.001
Severe COVID-19	2.066	1.612–2.647	<0.001
Malignancy	4.957	2.287–10.743	<0.001
Renal disease	3.059	1.932–4.843	<0.001
Diabetic ketoacidosis	5.062	2.638–9.713	<0.001
Hypertension	1.416	1.015–1.975	0.041
Chronic pulmonary diseases	2.140	1.133–4.040	0.019
Obesity	3.216	1.526–6.775	0.002
ICU for COVID-19	5.723	3.665–8.938	<0.001
MV for COVID-19	8.801	5.261–14.720	<0.001
Pulmonary mucormycosis	4.599	2.836–9.457	<0.001
Gastrointestinal mucormycosis	5.337	1.723–16.526	0.004

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COVID-19 ilişkili pulmoner mukormikoz (CAPM)

- Hindistan'da çok merkezli iki büyük çalışmada pulmoner mukormikoz COVID-19 öncesi %13.3 iken, pandemide %8.6 **(pandemide tanı güçlüğü, farkındalık???)**
- Hindistan, Fransa ve Şili'den elde edilen kısıtlı verilere göre CAPM'nin pooled prevalansının 10.000 hasta'da 5 olduğu tahmin edilmektedir.
- Kontrolsüz DM ve uygun olmayan steroid tx en büyük risk
- Klinik bulgu ile ddx .çok zor; sadece COVID-19 lu ve risk faktörleri taşıyan hastalarda, kahve-siyah balgam ve hemoptizi varlığında kuşkulanılmalı??
- Median COVID-19 sonrası 2-3 hft; tanı için bronkoskopi +

Definition, diagnosis, and management of COVID-19-associated pulmonary mucormycosis: Delphi consensus statement from the Fungal Infection Study Forum and Academy of Pulmonary Sciences, India

Panel 1: Definitions of COVID-19 associated pulmonary mucormycosis

COVID-19-associated pulmonary mucormycosis (CAPM) is diagnosed either simultaneously with or within 3 months of virologically confirmed COVID-19.

Proven CAPM

Histopathology or cytology showing aseptate hyphae or culture obtained by a sterile procedure from a usually sterile site (pleural fluid or lung) showing growth of Mucorales.

Probable CAPM

Presence of all the following: compatible clinical features, risk factors, and suggestive imaging (thick-walled cavity, large consolidation, reversed halo sign, or multiple large nodules) and demonstration of aseptate hyphae (with or without growth of Mucorales) in a sample representative of the lower respiratory tract (including bronchoalveolar lavage, non-bronchoscopic bronchial lavage, bronchial washings, bronchial brushing, endotracheal aspirates, and sputum).

Possible CAPM

Presence of all the following: compatible clinical features; uncontrolled diabetes, prolonged or inappropriate glucocorticoid therapy (dose, duration, or indication deviating from the current evidence-based practice for glucocorticoids in COVID-19); and highly suggestive radiology (reversed halo sign, mycotic aneurysm, or thick-walled cavity), in the absence of a definite alternative diagnosis.

Panel 2: CT findings of COVID-19-associated pulmonary mucormycosis

Highly suggestive

- Thick-walled cavity
- Reversed halo sign
- Large consolidation or necrotising pneumonia
- Mycotic aneurysm
- Bird's nest sign
- Multiple large nodules (nodules >1 cm)
- Serial imaging showing cavity with an air-fluid level

Suggestive

- Pleural effusion

Non-specific

- Pneumothorax

Not suggestive

- Enlarged mediastinal lymph nodes
- Centrilobular nodules or tree-in-bud appearance (could be seen in patients with haemoptysis or in patients with coexisting COVID-19-associated pulmonary aspergillosis)

Definition, diagnosis, and management of COVID-19-associated pulmonary mucormycosis: Delphi consensus statement from the Fungal Infection Study Forum and Academy of Pulmonary Sciences, India

Risk factors		
Uncontrolled diabetes	Yes	100%
Inappropriate steroid therapy	Yes	100%
Severe COVID-19	Yes	78%
Immunosuppression	Yes	95%
Immunomodulators for COVID-19 (eg, tocilizumab)	Yes	28%
Altered iron metabolism	Yes	78%
ICU admission for COVID-19	No	85%
Use of industrial oxygen, contaminated humidifier water, or reused masks	No	65%
No or irregular use of a mask during COVID-19 or post-COVID-19 period	No	79%
Zinc supplement for COVID-19	No	75%
Clinical features		
Fever	Suggestive	83%
Worsening or productive cough	Suggestive	87%
Brownish or black sputum	Highly suggestive	74%
Chest pain	Suggestive	71%
Haemoptysis	Highly suggestive	70%
Worsening respiratory symptoms patients with COVID-19	Suggestive	83%
Worsening chest imaging	Suggestive	70%

Evaluation of CAPM		
Characteristic imaging on CT with intravenous contrast	Yes	100%
Routine imaging of paranasal sinuses or brain	No	89%
Respiratory sample positive for Mucorales by conventional diagnostic techniques	Yes	100%
Bronchoalveolar lavage sample positive for Mucorales by molecular diagnostic techniques	Yes	74%
Serology	No	83%
Molecular test of blood, urine, or body fluid	No	58%

Diagnostic procedures		
Open-lung biopsy for diagnosis	No	73%
Diagnostic bronchoscopy should be performed as early as possible for the evaluation of suspected CAPM	Yes	95%
Flexible bronchoscopy can be safely performed in all patients with COVID-19 (intubated and non-intubated), following standard precautions	Yes	78%
CT-guided trucut biopsy (or fine-needle aspiration with on-site evaluation)	Yes	91%
Laboratory processing of samples		
Use of high-volume samples	Yes	85%
Rapid transport to the laboratory	Yes	90%
Use of Calcofluor microscopical examination	Yes	72%
Semiquantitative estimation of fungus	Not recommended	85%
Mincing (instead of grinding) the tissue sample	Yes	87%
PCR from surgical or biopsy specimens for bronchoalveolar lavage fluid	Yes	74%
The histopathology of CAPM is not different from non-CAPM	Yes	90%
Immunohistochemistry is useful in differentiating mucormycosis from aspergillosis in tissues	Yes	61%

COVID-19’un Mukormikoza getirdiği zorluklar

- Pulmoner mukormikoz tanısı, solunum örneklerinden veya bronkoskopiden kaçınma nedeniyle COVID-19 hastalarında büyük bir zorluktur. Pulmoner mukormikozdan sadece klasik risk gruplarındaki hastalarda (örneğin, hematolojik malignite, solid organ nakli ve otoimmün hastalıklar) değil, aynı zamanda COVID-19'lu olanlar da dahil olmak üzere diğer hasta gruplarında da şüphelenilmelidir.

- Toraks CT’de COVID-19 ve pulmoner mukormikoz bulgularının benzerliği; ddx güçlüğü (nodül ,periferal buzlı cam, konsolidasyon ve ters halo)
- Moleküler tanı yöntemlerine herzaman heryerden ulaşamama
- Gerçek prevelansını bilememek (Aspergillus dışı tüm küfler için geçerli)
- Pulmoner ve gastrointestinal mukormikoz tanısı zordur ve özellikle Hindistan'da ve diğer düşük gelirli ve orta gelirli ülkelerde sıklıkla gözden kaçabilir.

- *Diyabet ve COVID-19 insidansı yüksek bölgelerde ki hastalar iyileştikten 30 gün sonraya kadar mukormikoz semptomları açısından yakın takip edilmelidir.*

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ORIGINAL ARTICLE

mycoses WILEY

Treatment of pulmonary mucormycosis with adjunctive nebulized amphotericin B (MUCONAB trial): Results of an open-label randomized controlled trial

Abstract

Background: The role of nebulized amphotericin B (NAB) in managing pulmonary mucormycosis (PM) is unknown.

Methods: In this open-label trial, we randomized PM subjects to receive either intravenous liposomal amphotericin B (control arm, 3–5 mg/kg/day) alone or along with nebulized amphotericin B deoxycholate (NAB, 10 mg twice a day, every alternate day). The primary outcomes were: (1) overall response ('success' [complete or partial response] or 'failure' [stable disease, progressive disease, or death]) at 6 weeks; and (2) the proportion of subjects with adverse events (AE). The key secondary outcome was 90-day mortality. We performed a modified intention-to-treat (mITT) analysis where we included only subjects receiving at least a single dose of NAB.

Results: Fifteen and 17 subjects were randomized to the control and NAB arms; two died before the first dose of NAB. Finally, we included 30 subjects (15 in each arm; mean age 49.8 years; 80% men) for the mITT analysis. Diabetes mellitus ($n = 27$; 16/27 were COVID-19-associated PM) was the most common predisposing factor. The overall treatment success was not significantly different between the control and the NAB arms (71.4% vs. 53.3%; $p = .45$). Twenty-nine subjects experienced any AE, but none discontinued treatment. The 90-day mortality was not significantly different between the control (28.6%) and NAB arm (53.3%; $p = .26$).

Conclusion: Adjunctive NAB was safe but did not improve overall response at 6 weeks. A different dosing schedule or nebulized liposomal amphotericin B may still need evaluation. More research is needed to explore other treatment options for PM.

- LAMB + LAMB NAMB
- NAMB advers etki açısından güvenli ancak 90. gün mortalite her iki grupta da anlamlı fark yok

Species identification and antifungal susceptibility		
Does species identification help in the management?	Yes	74%
Is an antifungal susceptibility test essential for optimal therapy?	Yes	71%
Choice of drug and dose		
Liposomal amphotericin B is the treatment of choice for CAPM	Yes	100%
If liposomal formulation is unavailable, any lipid formulation can be used	Yes	100%
If no lipid formulation is available, amphotericin B deoxycholate should be used as the primary therapy over posaconazole or isavuconazole	Yes	94%
Initial dose of intravenous liposomal amphotericin B	5 mg/kg	80%
Should the amphotericin B dose be escalated in bilateral or non-operable disease?	No	85%
Should the amphotericin B dose be escalated in the presence of uncontrolled risk factors for CAPM?	No	90%
Should the amphotericin B dose be escalated in the presence of extrapulmonary mucormycosis (disseminated or ROCM)?	No	52%
After complete or partial response is achieved, maintenance treatment with isavuconazole or posaconazole should be given	Yes	100%
Preferred formulation of posaconazole is a tablet	Yes	80%
Therapeutic drug monitoring of posaconazole	Yes	74%

Combination of antifungals		
The combination of antifungals (posaconazole or isavuconazole with amphotericin) is not evidence based and should not be recommended	Yes	89%
Echinocandins in combination with amphotericin B can be given in CAPM	No	83%
Salvage therapy with posaconazole or isavuconazole might be considered in refractory patients	Yes	100%
Nebulised amphotericin B for CAPM	No	95%

Response monitoring and duration of therapy		
Duration of therapy should be based on response assessment (instead of a fixed duration)	Yes	81%
Monitoring with a weekly chest radiography (along with antifungals as and when required)	Yes	95%
Preferred timing of CT scan for response assessment	4–6 weeks	70%
Surgery For CAPM		
All patients with potentially resectable disease of the lung (unilateral) should undergo surgery	Yes	95%
Preoperative multidisciplinary team evaluation	Yes	100%
Timing of surgery after diagnosis*	As early as possible (< 1 week); <2 weeks	34%; 40%
Spirometry desirable in all patients preoperatively, especially before pneumonectomy or in those with pre-existing lung disease	Yes	100%
Surrogate tests such as 6-MWT or other methods are sufficient to assess exercise capacity (if spirometry not possible)	Yes	90%
Preoperative assessment of frailty	Yes	82%
Delay surgery or continue medical management and reassess in frail patients	Yes	89%
Surgery for CAPM in the presence of COVID-19-related lung disease†	After stabilistion	80%
Extensive invasion of mediastinal structures and hilar vessels seen on thoracic imaging is associated with technical difficulties during surgery and poor outcome; hence, initial medical management followed by reassessment is suggested	Agreed	81%

SCOPING REVIEW Open Access

Cryptococcus neoformans, a global threat to human health

Youbao Zhao[1*], Leixin Ye[2,3], Fujie Zhao[1], Lanyue Zhang[2,3], Zhenguo Lu[1], Tianxin Chu[1], Siyu Wang[1], Zhanxiang Liu[1], Yukai Sun[1], Min Chen[4], Guojian Liao[5], Chen Ding[6], Yingchun Xu[7], Wanqing Liao[4] and Linqi Wang[2,3*]

Abstract

Background Emerging fungal pathogens pose important threats to global public health. The World Health Organization has responded to the rising threat of traditionally neglected fungal infections by developing a Fungal Priority Pathogens List (FPPL). Taking the highest-ranked fungal pathogen in the FPPL, *Cryptococcus neoformans*, as a paradigm, we review progress made over the past two decades on its global burden, its clinical manifestation and management of cryptococcal infection, and its antifungal resistance. The purpose of this review is to drive research efforts to improve future diagnoses, therapies, and interventions associated with fungal infections.

Methods We first reviewed trends in the global burden of HIV-associated cryptococcal infection, mainly based on a series of systematic studies. We next conducted scoping reviews in accordance with the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews using PubMed and ScienceDirect with the keyword *Cryptococcus neoformans* to identify case reports of cryptococcal infections published since 2000. We then reviewed recent updates on the diagnosis and antifungal treatment of cryptococcal infections. Finally, we summarized knowledge regarding the resistance and tolerance of *C. neoformans* to approved antifungal drugs.

Results There has been a general reduction in the estimated global burden of HIV-associated cryptococcal meningitis since 2009, probably due to improvements in highly active antiretroviral therapies. However, cryptococcal meningitis still accounts for 19% of AIDS-related deaths annually. The incidences of CM in Europe and North America and the Latin America region have increased by approximately two-fold since 2009, while other regions showed either reduced or stable numbers of cases. Unfortunately, diagnostic and treatment options for cryptococcal infections are limited, and emerging antifungal resistance exacerbates the public health burden.

Conclusion The rising threat of *C. neoformans* is compounded by accumulating evidence for its ability to infect immunocompetent individuals and the emergence of antifungal-resistant variants. Emphasis should be placed on further understanding the mechanisms of pathogenicity and of antifungal resistance and tolerance. The development

HALK SAĞLIĞI PROBLEMİ;

- Son iki dekadda global bir artış
- 2009'dan bu yana Avrupa, Kuzey ve Latin Amerika'da X2 kat artış
- Tanı ve tedavi opsiyonlarının kısıtlılığı
- İmmünkompetan hastalarda+
- Antifungal direnç !

COVİD-19 öncesi ve sonrası Kriptokokkoz

- 2000-2012 yılları Brezilya %75 altta HIV+; %5.5 diğer immünsüpresif nedenler
- Küresel ve bölgesel artış 2007, 2014 ve 2020'de HIV ile ilişkili CM, HIV ile enfekte kohortlarda insidans verileri (Birleşmiş Milletler HIV/AIDS Ortak Programından) ve nüfusa dayalı HIV etki değerlendirme araştırmalarında bildirilmiştir.

- Altta yatan en az bir immünsüpresif durum
- %82 de steroid kullanımı
- %53 mortalite ile ÖNCEYE göre yükseklik (COVID-19 ile beraber çoklu risk faktörleri
- Kriptokoklardan salınan proteaz, üreaz , fosfolipaz SARSCoV2'de hiperinflamasyon pro active ediyor???
- COVID-19 ve SOT hastalarında Th disregülasyonu

Zhao et al. Infectious Diseases of Poverty (2023) 12:20

Alves Soares E, et al PLoS Negl Trop Dis. 2019; 13 (7), e0007569.

Le Infezioni in Medicina, n. 1, 6-12, 2023

Kriptokokkoz

- 20 den fazla tür
- İnsan mikrobiyatasına ait olmasa da KOAH lı hastalarda kolonizasyon
- Toprakta bulunur, insanlara giriş yolu akciğer
- Ağır COVID-19'lu hastalar, azalmış lenfopeni ve CD4+ ve CD8+ T lenfosit sayısı ile ilişkili sitokin seviyelerinde değişiklik (IL-2, IL-6, IL-10, IFN-y) nedeniyle kriptokokoz duyarlılığı artırabilir

Le Infezioni in Medicina, n. 1, 6-12, 2023
doi: 10.53854/liim-3101-2

Invasive cryptococcal disease in COVID-19: systematic review of the literature and analysis

- 32 hasta
- Hastaneye kabulden ortalama 22 gün sonra
- 23/25 kan, 17/21 BOS, 7/7 BAL
- Başlıca komorbidite ;HT; SOT,DM
- 3 hasta HIV +; 3 hasta Siroz;
- ARDS; YBÜ takibi ve uygunsuz tedavi mortalite ile ilişkili

CACI (COVID-19 ilişkili Kriptokok İnfeksiyonları)

Infection (2022) 50:1007–1012
https://doi.org/10.1007/s15010-022-01805-y

BRIEF REPORT

COVID-19-associated *Cryptococcus* infection (CACI): a review of literature and clinical pearls

Dinesh Regalla[1] · Mollie VanNatta[2] · Mohammad Alam[1] · Alexandre E. Malek[1]

Received: 3 November 2021 / Accepted: 9 March 2022 / Published online: 24 March 2022

Abstract

Background Cryptococcal infection has been increasingly reported in patients with COVID-19 infection, but the epidemiological factors, presentation, diagnostic certainty, and outcome have not been well-described.

Methods We reviewed the published cases of COVID-19-associated *Cryptococcus* infections (CACI) to shed the light on the burden of this infection.

Results We identified 13 patients with confirmed cryptococcal infection. *Cryptococcus* infection was primarily seen in patients with severe COVID-19 disease who received corticosteroids therapy and admitted to the intensive care unit. Pulmonary CACI was the most common reported infection followed by cryptococcal meningitis.

Conclusion In light of the high mortality rate, clinicians should maintain a high clinical suspicion of CACI in critically ill patients.

- Steroid alan ve YBÜ de takip edilen ağır COVID-19 olgularında
- En sık kriptokok menenjitini pulmoner CACI

Variable	Cryptococcosis following COVID-19 ($n = 65$)	COVID-19 without cryptococcosis ($n = 212,414$)	p value
Age at index event (years), mean (SD)	56.8 (14.5)	56 (22.4)	.7692
Male sex	52 (80)	108,802 (51)	<.0001
BMI (kg/m^2), mean (SD)	26.8 (6.93)	29.3 (7.69)	1036
Race			
White	41 (63)	144,234 (68)	.4047
Black or African American	17 (26)	41,868 (20)	.1917
Asian	0 (0)	410,916 (2)	.2571
Unknown race	10 (15)	20,982 (10)	.1368
Ethnicity			
Hispanic or Latino	14 (22)	29,260 (14)	.0694
Non-Hispanic	48 (74)	161,555 (76)	.6763
Underlying comorbidities			
HIV	21 (32)	3461 (2)	<.0001
Transplanted organs or tissues	18 (28)	5659 (3)	<.0001
Neoplasm	17 (26)	46,629 (22)	.4132
Immunodeficiency with predominantly antibody defects	10 (15)	589 (<1)	<.0001
Combined immunodeficiencies	0 (0)	67 (<1)	.8861
Common variable immunodeficiency	0 (0)	137 (<1)	.8377
Other immunodeficiencies	21 (32)	5592 (3)	<.0001
Sarcoidosis	10 (15)	981 (<1)	<.0001
Systemic connective tissue disorders	10 (15)	8378 (4)	<.0001
Rheumatoid arthritis	10 (15)	596 (<1)	<.0001
Non-infective enteritis and colitis	10 (15)	10,007 (5)	<.0001
Hepatic fibrosis and cirrhosis	10 (15)	5351 (3)	<.0001
Type 2 diabetes mellitus	27 (42)	64,126 (30)	.0463
Heart failure	18 (28)	36,674 (17)	.0262
Malnutrition	17 (26)	11,436 (5)	<.0001
Chronic kidney disease	26 (40)	51,074 (24)	.0026
Laboratory values			
Leukocytes (K/µl), mean (SD)	9.18 (6.9)	9.11 (21.8)	.9818
Lymphocytes (K/µl), mean (SD)	1.97 (4.31)	3.68 (10.5)	.3472
CD4 cells (cells/µl), mean (SD)	73 (68.9)	299 (316)	.0242
AST (units/L), mean (SD)	80.3 (235)	58.2 (256)	.5582
ALT (units/L), mean (SD)	85.1 (393)	45.4 (157)	.0769
Alkaline phosphatase (units/L), mean (SD)	139 (141)	101 (101)	.0097
Serum creatinine (mg/dl)	1.61 (1.37)	1.36 (1.79)	.2923
Albumin (mg/dl), mean (SD)	3.02 (0.767)	3.46 (0.665)	<.0001
Haemoglobin A1C (%), mean (SD)	7.34 (2.46)	7.29 (2.36)	0.9404
Ferritin (ng/ml), mean (SD)	5253 (17950)	941 (2344)	<.0001
C-reactive protein (mg/dl), mean (SD)	81.7 (84.3)	79.4 (82.6)	.8972
Lactate dehydrogenase (units/L)	1006 (1798)	433 (501)	<.0001

Sadece HIV ve nakil hastaları DEĞİL; literatürü destekler nitelikte diğer imm. süpresif durumların varlığı (diğer çalışmalarda %56 COVID-19 öncesi dönemdeki risk faktörlerinin olmadığını göstermişti.)

COVID-19 sonrası gelişen kriptokokkoz multifaktöryel;

- Epidemiyolojik risk faktörlerinin artması
- Latent kalabilmesi ve T hücre defektleri
- Ağır COVID-19 ve kullanılan immunmodülatör ajanlar

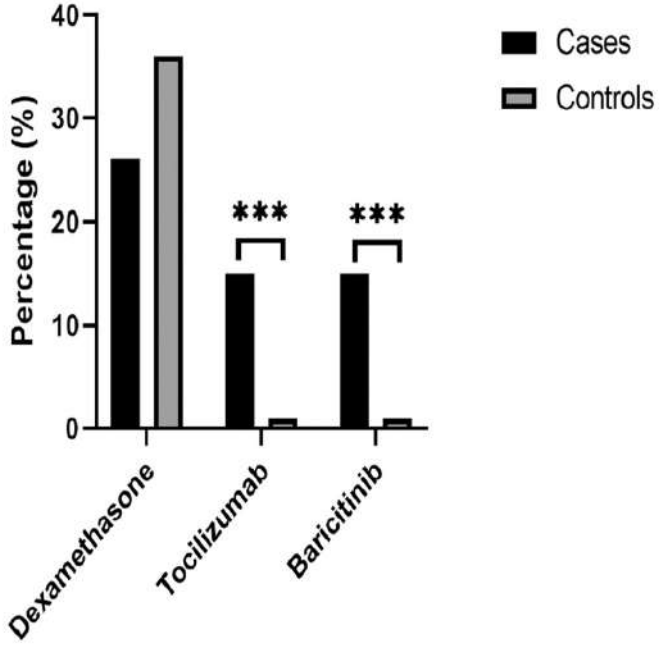
ORIGINAL ARTICLE

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases WILEY

Cryptococcosis among hospitalised patients with COVID-19: A multicentre research network study

- 212479 hastada kriptokokkoz insidansı %0.022 (65 hasta)
- COVID-19 hastalarında düşük kriptokokoz insidansı bu popülasyonda tanıdaki aksaklıklar???
- CD4+ hücre sayısında azalma; hücresel immün cevapta defekt
- Kriptokokozlu hastalarda daha yüksek yoğun bakıma yatış oranları, MV ve mortalite

- COVID-19 tedavisinde kullanılan immünomodülatör ajanlar kriptokokoza duyarlılığı arttırır.
- İlk infeksiyondan sonra, belirgin klinik semptomlara neden olmadan pulmoner granülom
- Kortikosteroidlerin uygulanması alveoler makrofajların bağlanma ve fagositik fonksiyonunu bozar ve mantar yükünü artırır.
- Ekstrapulmoner yayılımı kolaylaştırır.
- Steroid maruziyeti kriptokokkoz gelişen ve gelişmeyen hastalarda daha önce yayınlanmış 9 çalışmanın aksine her iki grupta benzer oranda bulunmuş.



Invasive Fusariosis in Nonneutropenic Patients, Spain, 2000–2015

Invasive fusariosis (IF) is associated with severe neutropenia in patients with concurrent hematologic conditions. We conducted a retrospective observational study to characterize the epidemiology of IF in 18 Spanish hospitals during 2000–2015. In that time, the frequency of IF in nonneutropenic patients increased from 0.08 cases per 100,000 admissions in 2000–2009 to 0.22 cases per 100,000 admissions in 2010–2015. Nonneutropenic IF patients often had nonhematologic conditions, such as chronic cardiac or lung disease, rheumatoid arthritis, history of solid organ transplantation, or localized fusariosis. The 90-day death rate among nonneutropenic patients (28.6%) and patients with resolved neutropenia (38.1%) was similar. However, the death rate among patients with persistent neutropenia (91.3%) was significantly higher.

COVID-19 Öncesi

- Non nötropenik hastalarda yıllara göre belirgin artış
- Hematolojik komorbiditesi olmayan hastalarda
- Persistan nötropenisi olanlarda mortalite daha yüksek
- Bölgesel farklılıklar ve lokal epidemiyoloji önemli (SP, Fr)

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 27, No. 1, January 2021

Invasive Fusariosis in Nonneutropenic Patients, Spain, 2000–2015

per 100,000 admissions (p = 0.06). We observed a 3-fold increase in the incidence of IF in nonneutropenic patients, from 0.08 to 0.22 cases per 100,000 admissions (p = 0.05). This increase might have been caused by an increase in the at-risk population, environmental exposure to *Fusarium* conidia, the increased use of antifungal prophylaxis, or a combination of these factors.

COVID-19 Öncesi

Nötropenik olmayanlarda yıllar içinde artışın nedenleri;
*Zamanla risk altındaki popülasyon
*Çevresel fusarium konidya maruziyeti
*Antifungal kullanımı

Fusariosis

- Birkaç COVID-19 ile ilişkili fusariosis vakası bildirilmiştir
- Vaka raporları sayısı az olduğu için risk faktörleri , hakkında geniş sonuçlar çıkarılamaz.
- Hiçbir hastada COVID-19 dışındaki durumlarla ilişkili önemli immün yetmezlik yoktu
- Tüm hastalara kan veya balgam kültürleri alınarak tanı konuldu .
- Hepsinde akciğer parankimi tutulumu
- Sistemik antifungal ile tedavi edildi.

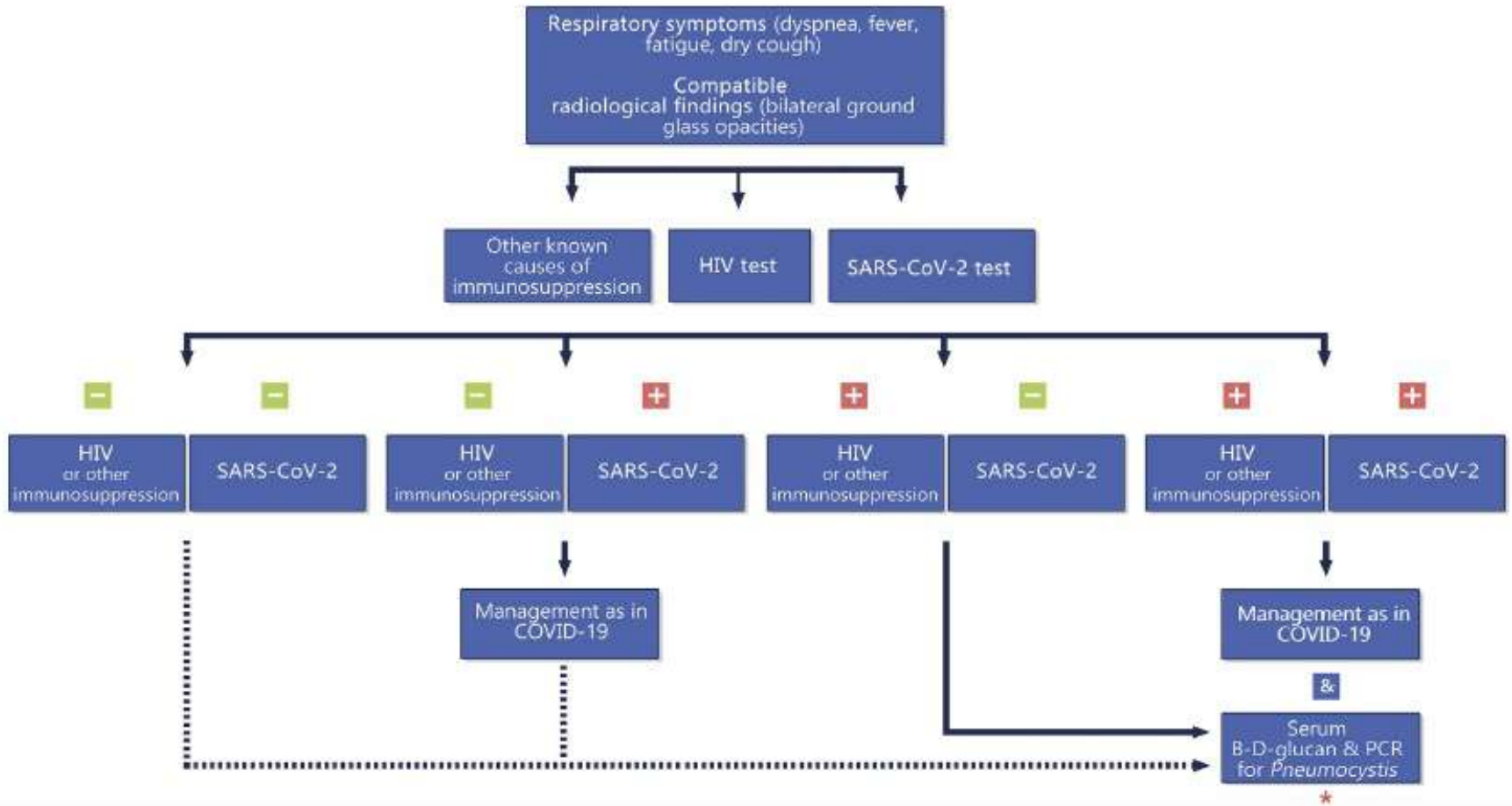
Pnömosistosis (PJP)

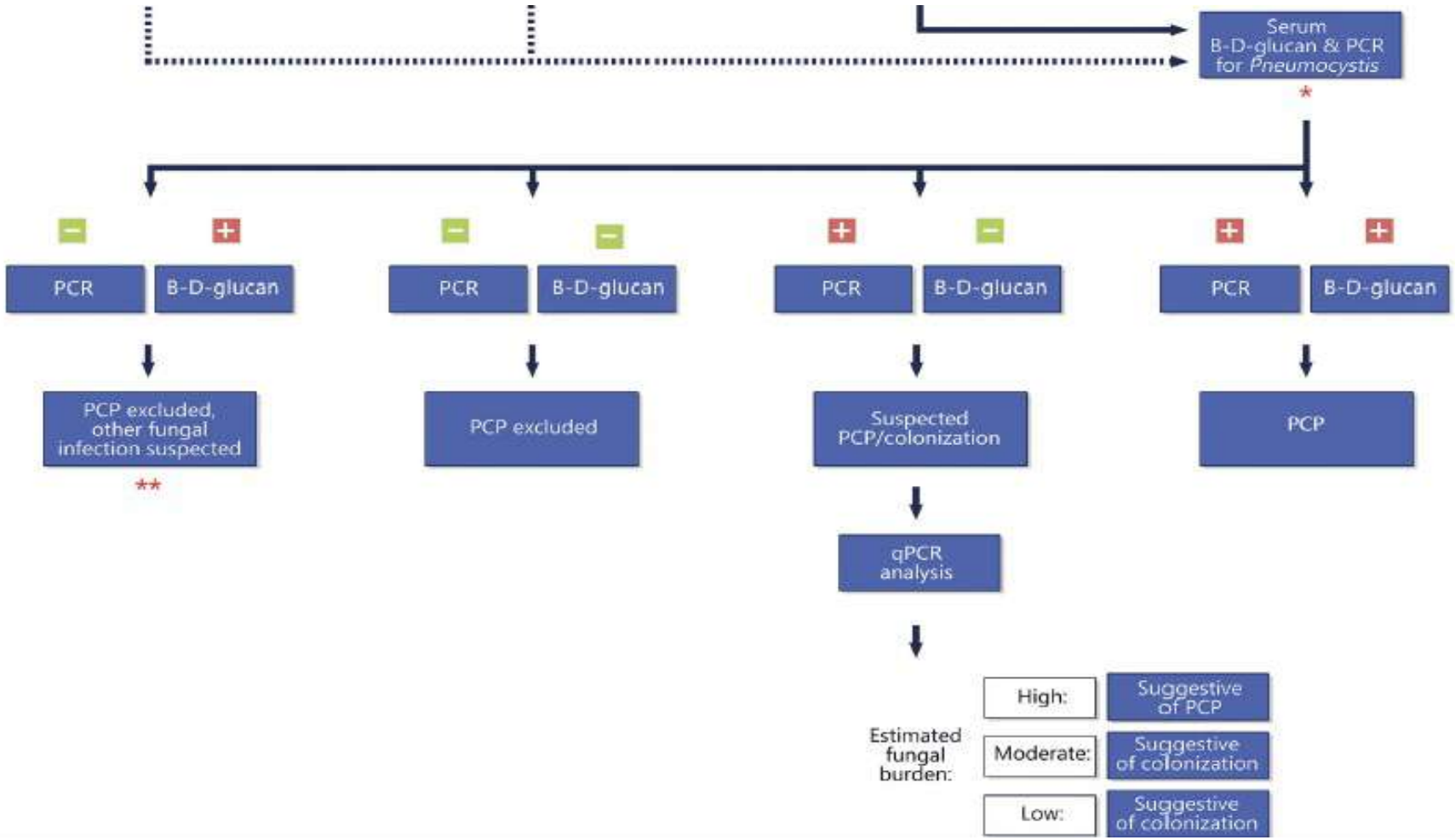
- Birkaç COVID-19 ile ilişkili *Pneumocystis jirovecii* vakası
- Genelde vakalar yaşlı hastalarda (ortalama yaş 78)
- Altta yatan bir HIV, malignite veya kronik steroid kullanım gibi bağışıklığı baskılayan durum.
- Şiddetli COVID-19 ile Pneumocystis pnömonisi (PJP) klinik olarak ayırt edilmesi güç
- Her iki klinik tabloda da bilateral buzlu cam opasiteleri ve lenfopeni mevcuttur
- Bildirilen tüm PJP koenfeksiyonu vakalarında laktat dehidrojenaz seviyeleri ve beta-D-glukan artışı ve lenfopeni (+)
- COVID-19'den genellikle 2 ila 21 gün sonra solunum örnekleri PCR (+)ile tanı konur.

(Kontaminasyon ve kolonizasyon ddx ÖNEMLİ)

- PJP'nin COVID-19'da tedavisi, standart; trimetoprim-sülfametoksazol rejimi ve steroidler
- Mortalite %42 ila %100 arasında.
- Profilaktik trimetoprim-sülfametoksazol kullanımı pozitif Pneumocystis testi PJP tanısı olan net olmayan COVID-19 hastalarında tartışmalı olmaya devam ediyor

Current Fungal Infection Reports (2022) 16:87–97


Respiratory symptoms (dyspnea, fever, fatigue, dry cough)
Compatible radiological findings (bilateral ground glass opacities)
Other known causes of immunosuppression
HIV test
SARS-CoV-2 test
−
−
−
+
+
−
+
+
HIV or other immunosuppression
SARS-CoV-2
HIV or other immunosuppression
SARS-CoV-2
HIV or other immunosuppression
SARS-CoV-2
HIV or other immunosuppression
SARS-CoV-2
Management as in COVID-19
Management as in COVID-19
&
Serum B-D-glucan & PCR for Pneumocystis
*


Serum
B-D-glucan & PCR
for *Pneumocystis*
*
PCR
B-D-glucan
PCR
B-D-glucan
PCR
B-D-glucan
PCR
B-D-glucan
PCP excluded,
other fungal
infection suspected
**
PCP excluded
Suspected
PCP/colonization
PCP
qPCR
analysis
Estimated
fungal
burden:
High:
Suggestive
of PCP
Moderate:
Suggestive
of colonization
Low:
Suggestive
of colonization

Scedosporium

- COVID ile ilişkili Scedosporium veya Lomentaspora enfeksiyonları nadir
- Şili'de COVID-19 ve İFİ hasta olgu serisinde sadece birinde *Scedosporium* raporlanmıştır.
- Ancak tanısal sınırlamalardan kaynaklı bu bildirimler eksik olabilir
- Bununla birlikte, *Scedosporium* veya *Lomentaspora* bağışıklığı baskılanmış hastalarda önemli fırsatçı patojenlerdir ve COVID-19'lu hastalarda bu türlerle fırsatçı enfeksiyonlar düşünülmelidir !

Teşekkürler