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# Mucormycosis

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# Disclosures

- The speaker declares no conflict of interest.

# Background

- The prevalence of mucormycosis is very high in Asian countries especially in uncontrolled diabetic patients of India and China
- Globally, rising mucormycosis cases
  - **INDIA:** from 24.7 cases per year (1990–2007) to 89 cases per year (2013–2015)
  - **IRAN:** from 9.7% in 2008 to 23.7% in 2014
  - **JAPAN:** from 0.01% mucormycosis cases in 1969 to 0.16% of cases in 1989
- Isolated renal mucormycosis in apparently healthy hosts is an intriguing disease in India and China



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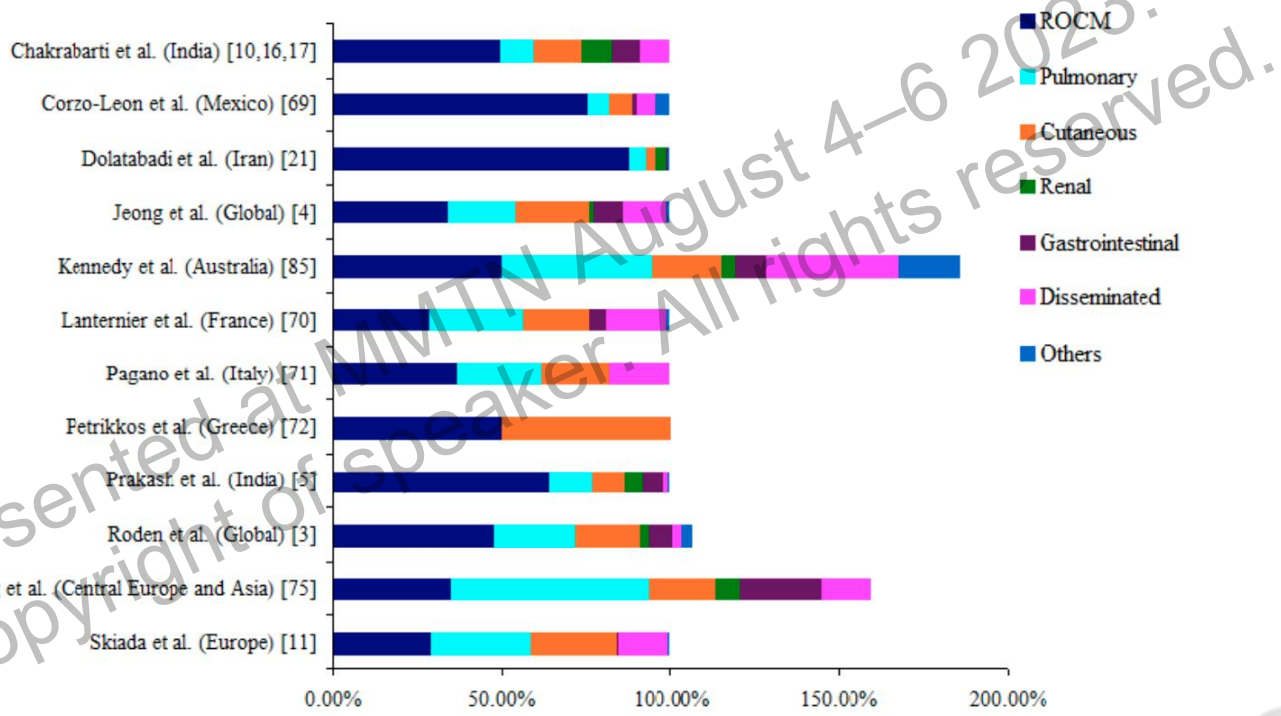
Prakash H, et al. Med Mycol. 2019;57(4):395–402. Dolatabadi S, J Mycol Med. 2018;28:269–73. , Yamazaki T, J Clin Microbiol. 1999;37:1732–8

# Forms of Mucormycosis: Global



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Prakash, H.; Chakrabarti, A. Global Epidemiology of Mucormycosis. *J. Fungi* 2019, *5*, 26.

# Forms of Mucormycosis: India




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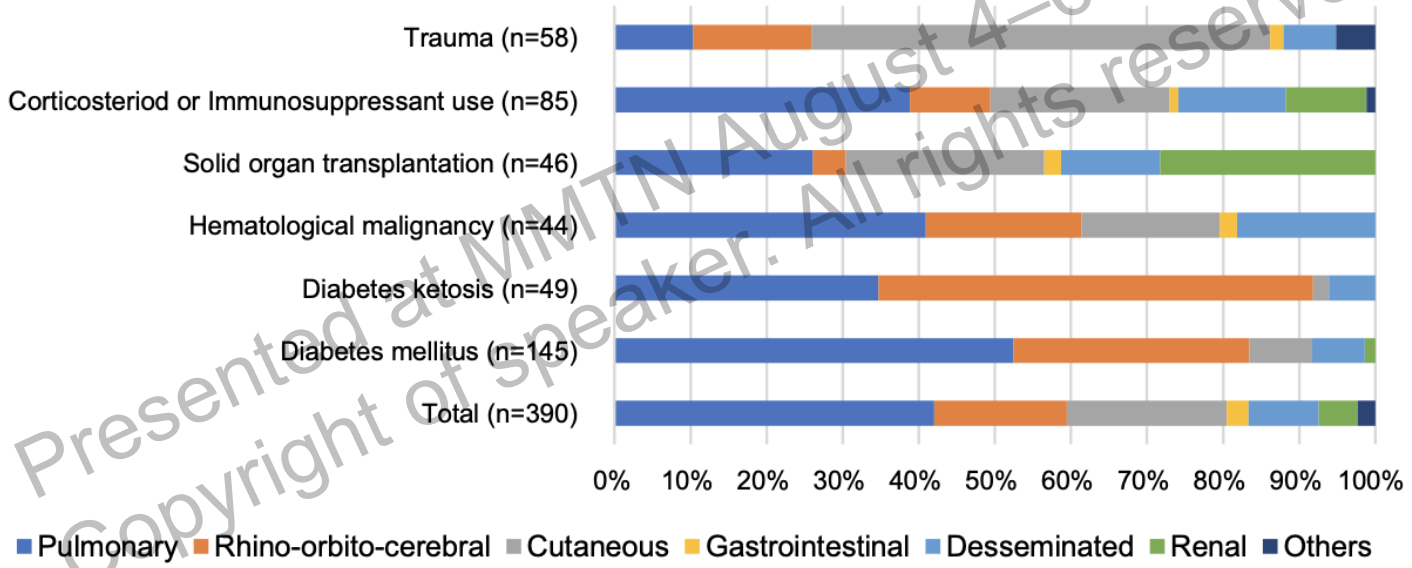
Prakash,H.;Chakrabarti, A. Epidemiology of Mucormycosis in India. Microorganisms 2021, 9, 523

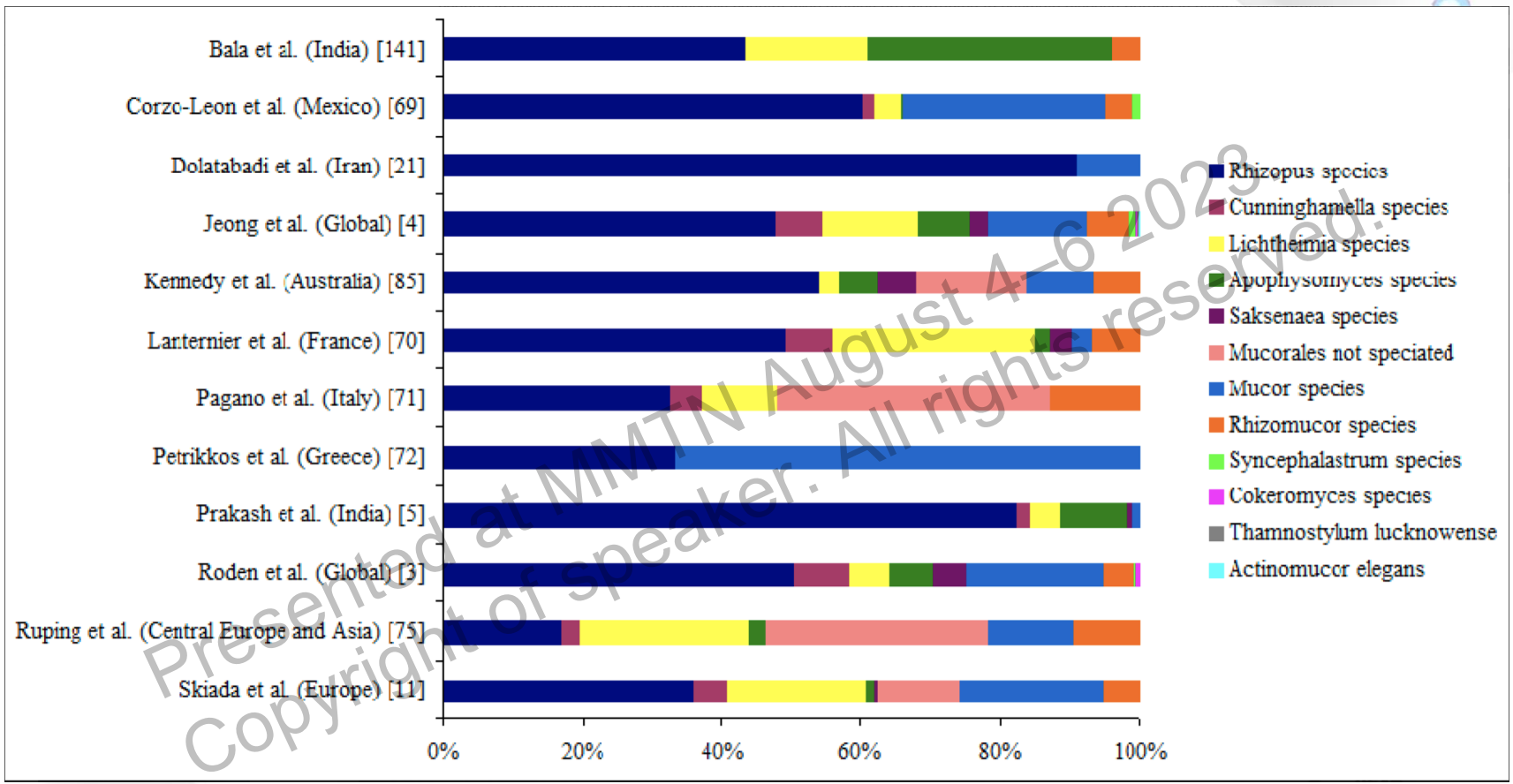
Mycopathologia (2022) 187:1–14
https://doi.org/10.1007/s11046-021-00607-4

ORIGINAL ARTICLE

# Mucormycosis in Mainland China: A Systematic Review of Case Reports

Lin-Wei Wei · Pei-Qiu Zhu · Xiao-Qing Chen · Jin Yu





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Prakash, H.; Chakrabarti, A. Global Epidemiology of Mucormycosis. *J. Fungi* 2019, *5*, 26.

# Species isolated from clinical specimen

**Table 2.** Causative agents of mucormycosis in India.

| ^ Causative Agents | Chakrabarti et al., 2001; 2006; 2009 [14–16] | Manesh et al., 2019 [17] | Chander et. al., 2018 [22] | Prakash et al., 2019 [5] | Patel et al., 2020 [6] | Priya et al., 2020 [18] |
|---|---|---|---|---|---|---|
| Total number of isolated Mucorales | 120 $ | 184 | 60 | **239** | **290** | **25** |
| *Rhizopus* species | 79 (65.8) [a] | 143 (77.7) | 28 (46.7) | 193 (80.8) | 231 (79.7) | 14 (56) |
| *Rhizopus arrhizus* | 74 (61.7) [a] | 91 (49.5) | 17 (28.3) | 124 (51.9) | 176 (60.7) | - |
| *Rhizopus microsporus* | 4 (4.2) [b] | 32 (17.4) | 9 (15) | 30 (12.6) | 32 (11) | - |
| *Rhizopus homothallicus* | 1 (3.1) [c] | - | 2 (3.3) | 6 (2.5) | 22 (7.6) | - |
| *Apophysomyces* species | 31 (25.8) [a] | 20 (10.9) | 13 (21.7) | 22 (9.2) | 23 (7.9) | 5 (20) |
| *Lichtheimia* species | 3 (5.3) [d] | 1 (0.5) | 8 (13.3) | 10 (4.2) | 10 (3.5) | 1 (4) |
| *Saksenaea* species | 3 (3.4) [e] | 1 (0.5) | 5 (8.3) | 2 (0.8) | 2 (0.7) | - |
| *Cunninghamella* species | - | 1 (0.5) | - | 5 (2.1) | 3 (1) | - |
| *Mucor* species | 1 (4) [f] | 4 (2.2) | 1 (1.7) | 3 (1.3) | 16 (5.5) | 3 (12) |
| *Rhizomucor* species | 2 (2.3) [e] | 1 (0.5) | 1 (1.7) | - | 4 (1.4) | - |
| *Syncephalastrum* species | 1 (3.1) [c] | 1 (0.5) | 4 (6.7) | - | 1 (0.4) | - |
| Nonsporulating Mucorales/other fungi | - | 12 (6.5) | - | 4 (1.7) | - | 2 (8) |



Prakash,H.;Chakrabarti, A. Epidemiology of Mucormycosis in India. *Microorganisms* 2021, *9*, 523

RESEARCH

# Clinical and Mycologic Characteristics of Emerging Mucormycosis Agent *Rhizopus homothallicus*

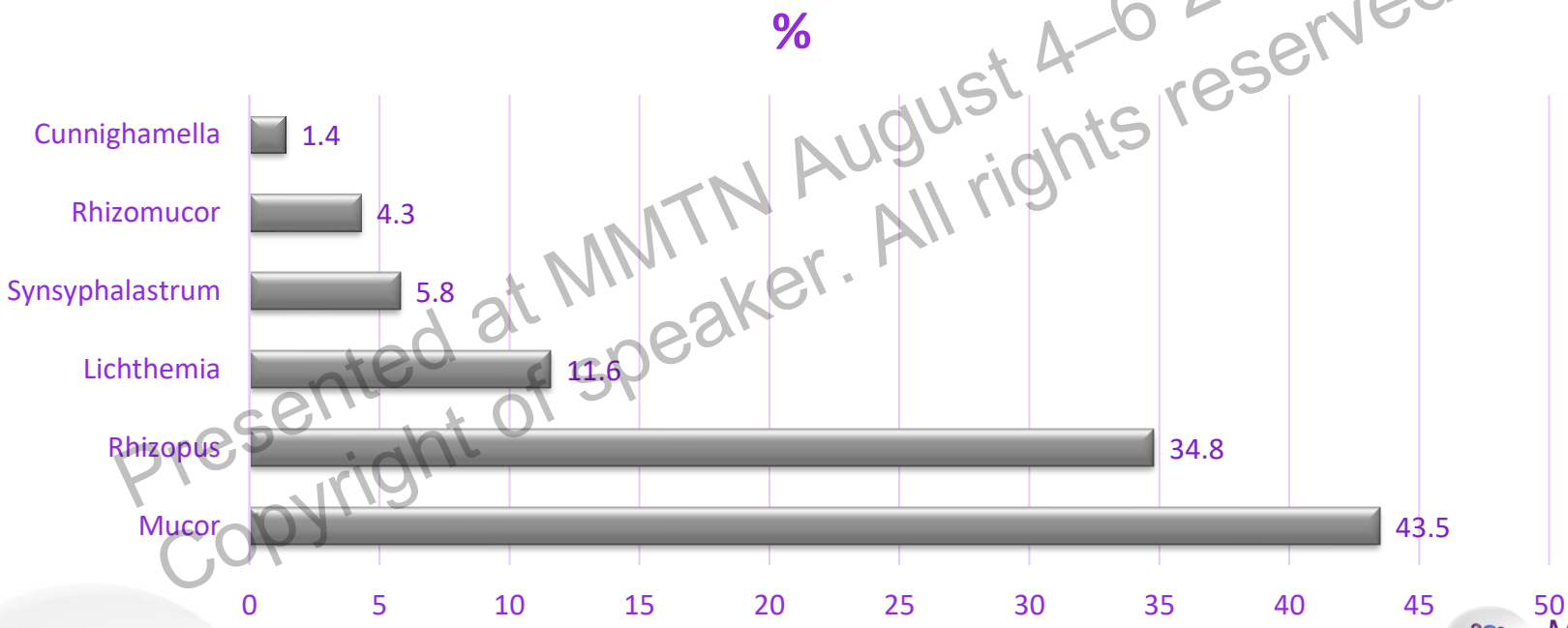
Shivaprakash M. Rudramurthy,[1] Shreya Singh,[1,2] Rimjhim Kanaujia, Hansraj Chaudhary,[3] Valliappan Muthu, Naresh Panda, Abhishek Pandey, Sheetal Thakur, Harsimran Kaur, Anup Ghosh, Ritesh Agarwal, Arunaloke Chakrabarti[1]

- *R. homothallicus* accounted for 43 (6.8%) of the 631 cases of mucormycosis
- *R. homothallicus* was independently associated with better survival (OR 0.08 [95% CI 0.02–0.36]; p = 0.001) than for *R. arrhizus* infection (4/41 [9.8%] vs. 104/266 [39.1%]) after adjusting for age, intracranial involvement, and surgery
- Antifungal-susceptibility testing: Amphotericin B [0.03–16], Itraconazole [0.03– 16], Posaconazole [0.03–8], and Isavuconazole [0.03–16]



Shivaprakash M. Emerging Infectious Diseases, Vol. 29,No. 7, July 2023, 1313-22

# Species of isolated Mucorales in 69 cases (China)






Wei, LW. Mucormycosis in Mainland China: A Systematic Review of Case Reports. *Mycopathologia* 187, 1–14 (2022).

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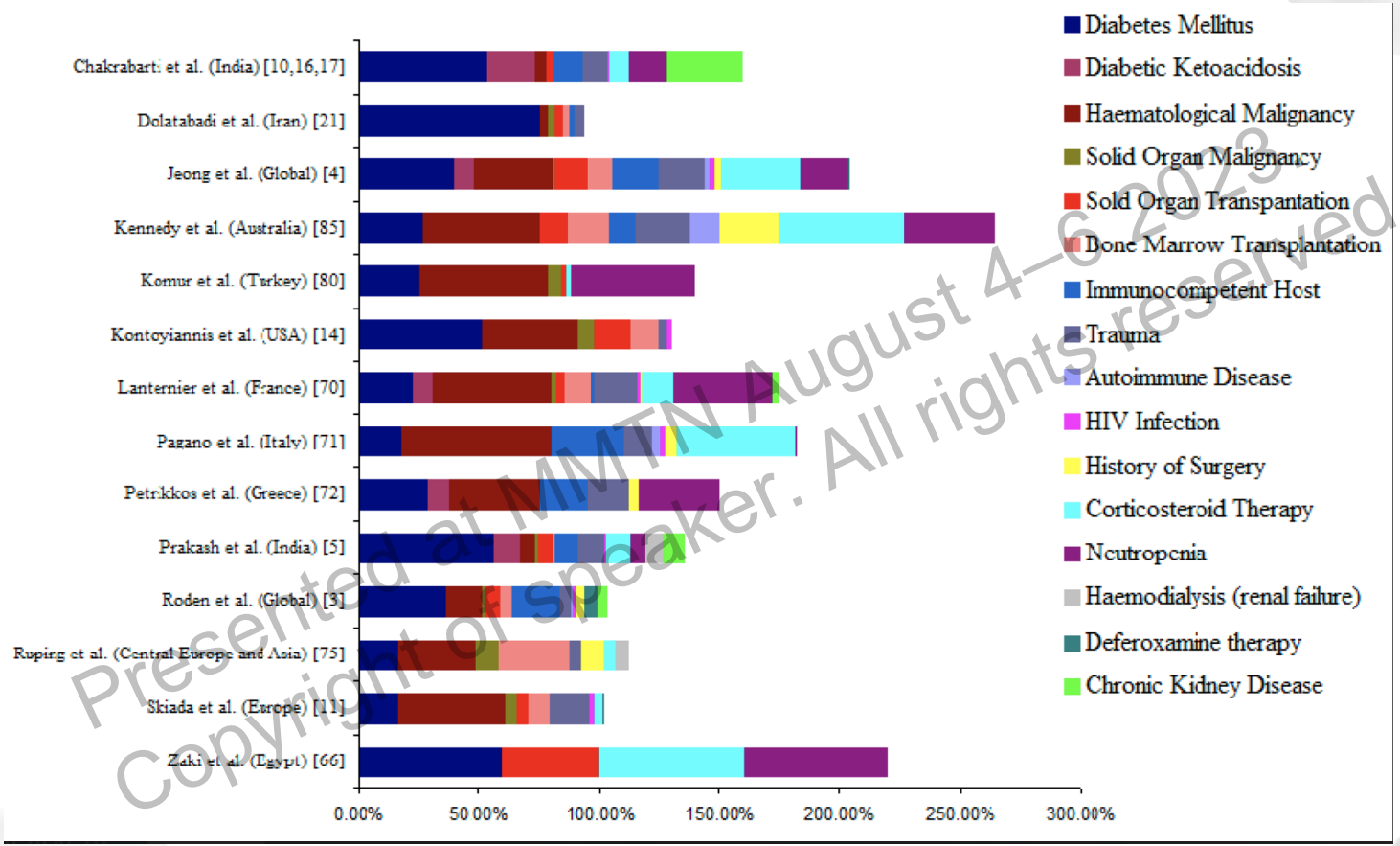






**Prakash, H.; Chakrabarti, A. Global Epidemiology of Mucormycosis. *J. Fungi* 2019, *5*, 26.**

# Mucormycosis in patients without immune defects

- In India, 3–26% of mucormycosis cases are recorded from the immunocompetent host
  - Cutaneous (necrotising fasciitis) following road traffic accidents
  - Isolated renal mucormycosis



CIDSCON 2018


Prakash,H.;Chakrabarti, A. Epidemiology of Mucormycosis in India. *Microorganisms* 2021, *9*, 523

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# Isolated renal mucormycosis in healthy adults

| Features | SGPGI (n=10) | PGIMER (n=15) |
|---|---|---|
| Study period | 2009-2016 | 2012-2017 |
| Underlying risk factors | None | None |
| Age (years), mean | 10 – 42 (24.7) | 16 – 50 (35.93) |
| Gender (Male) | 100% | 86.66% |
| Species | 6/10 had isolates, 3; *Rhizopus*, 3; *A. elegans* | 4/15, all *Rhizopus arrhizus* |
| Renal involvement | Bilateral | 11 unilateral, 4 bilateral |
| Mortality | 50% | 40% |
| Rural area, lower socioeconomical strata | | |





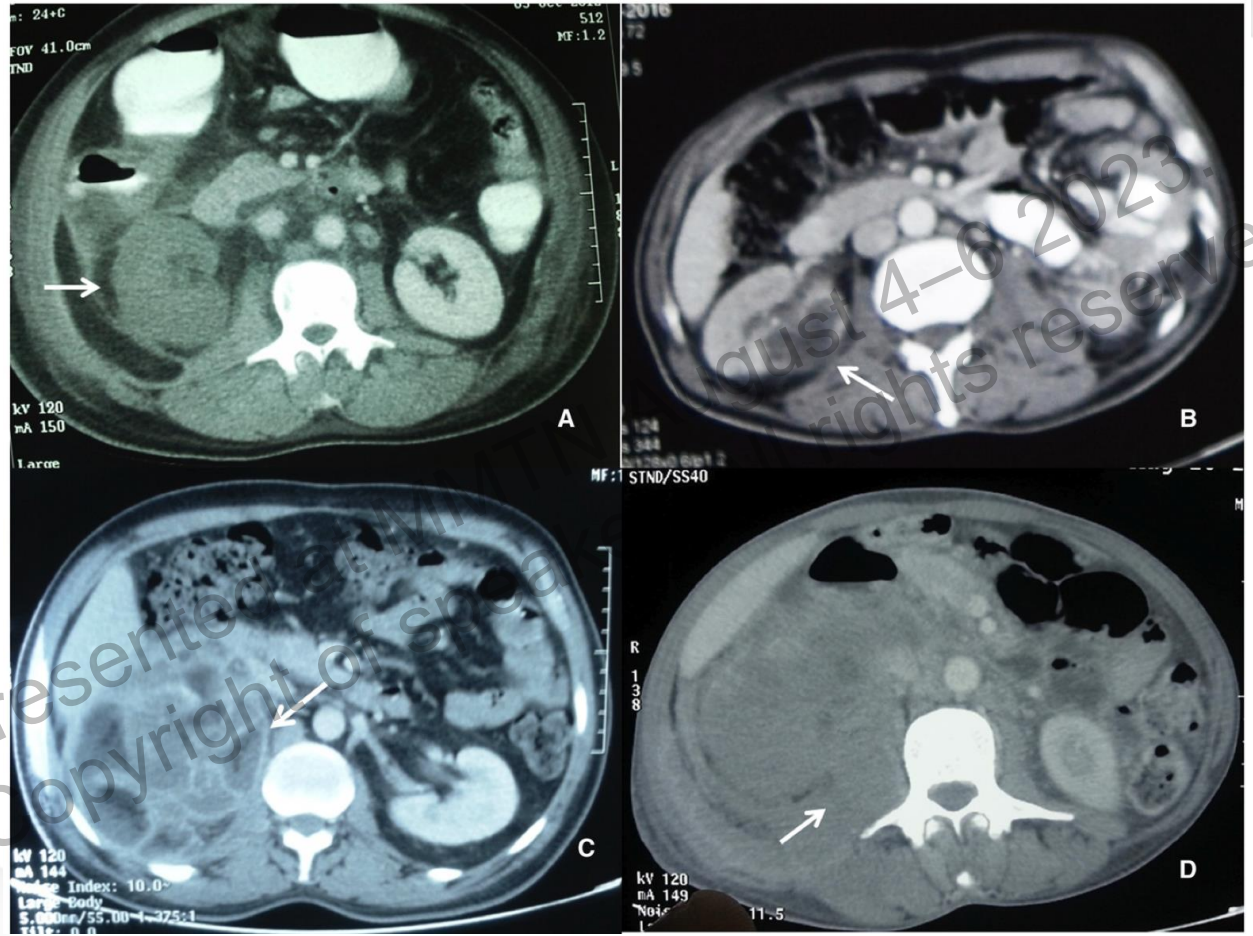
Devana SK. Am J Trop Med Hyg. 2019 Apr;100(4):791-797. Bhadauria D. Clinical Kidney Journal, 2018, vol. 11, no. 6, 769–776

# Isolated renal mucormycosis in healthy adults

- **Symptoms:** Fever, flank pain, sepsis, oliguria/anuria, AKI
- Repeated sterile urine and blood cultures, urine exam may show presence of mycelia
- Radio-imagings (USG/CT): bulky kidneys with areas of necrosis/ infarction, renal vessel thrombosis, thickened PC system, diffuse or patchy areas of absent or attenuated contrast enhancement with thickened Gerota's fascia, perinephric fat stranding. Bulky psoas muscle, adjacent organ involvement (spleen, colon)
- Amphotericin plus nephrectomy, Amphotericin local treatment through PCNL



Devana SK. Am J Trop Med Hyg. 2019 Apr;100(4):791-797. Bhadauria D. Clinical Kidney Journal, 2018, vol. 11, no. 6, 769–776






Devana SK. Am J Trop Med Hyg. 2019 Apr;100(4):791-797.

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Original Article

# Renal mucormycosis presenting during the COVID-19 pandemic: A series of 11 cases from a tertiary care center in India

**Vijay Kumar Sarma Madduri, Rahul Jena*, Gaurav Baid, Gautam Ram Choudhary, Arjun Singh Sandhu**

Department of Urology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

*E-mail: jena.rahul@gmail.com

- March to September 2021
- n=11, 8 male, Age: < 50 year (81.8%)
- 2 patients had underlying risk factor (DM and ulcerative colitis on steroid)
- 4 patients had H/O COVID-19 in past 6 months
- Mortality: 45.5%



Madduri VKS. Indian J Urol. 2022 Apr-Jun;38(2):115-120

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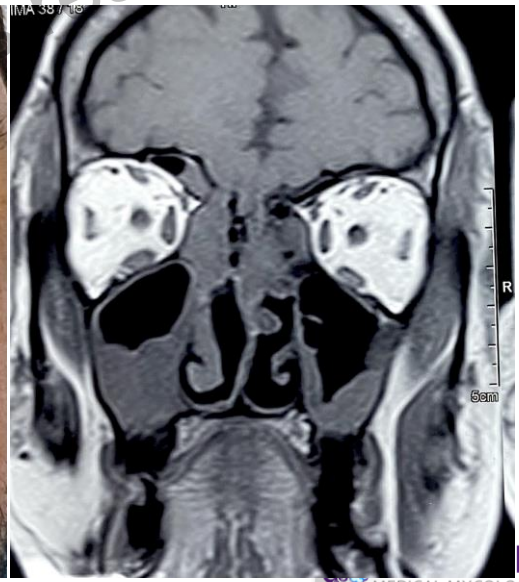
# Diagnostic challenge:

- Clinical features are nonspecific
- Delay in diagnosis

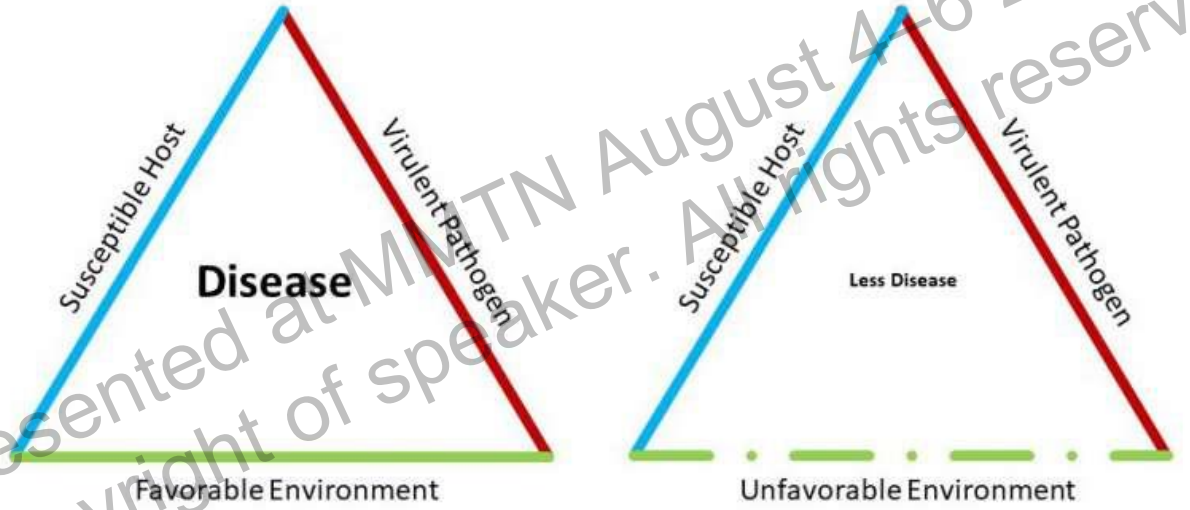








Pictures from my personal collection

# COVID-19 Pandemic: Epidemiological triangle



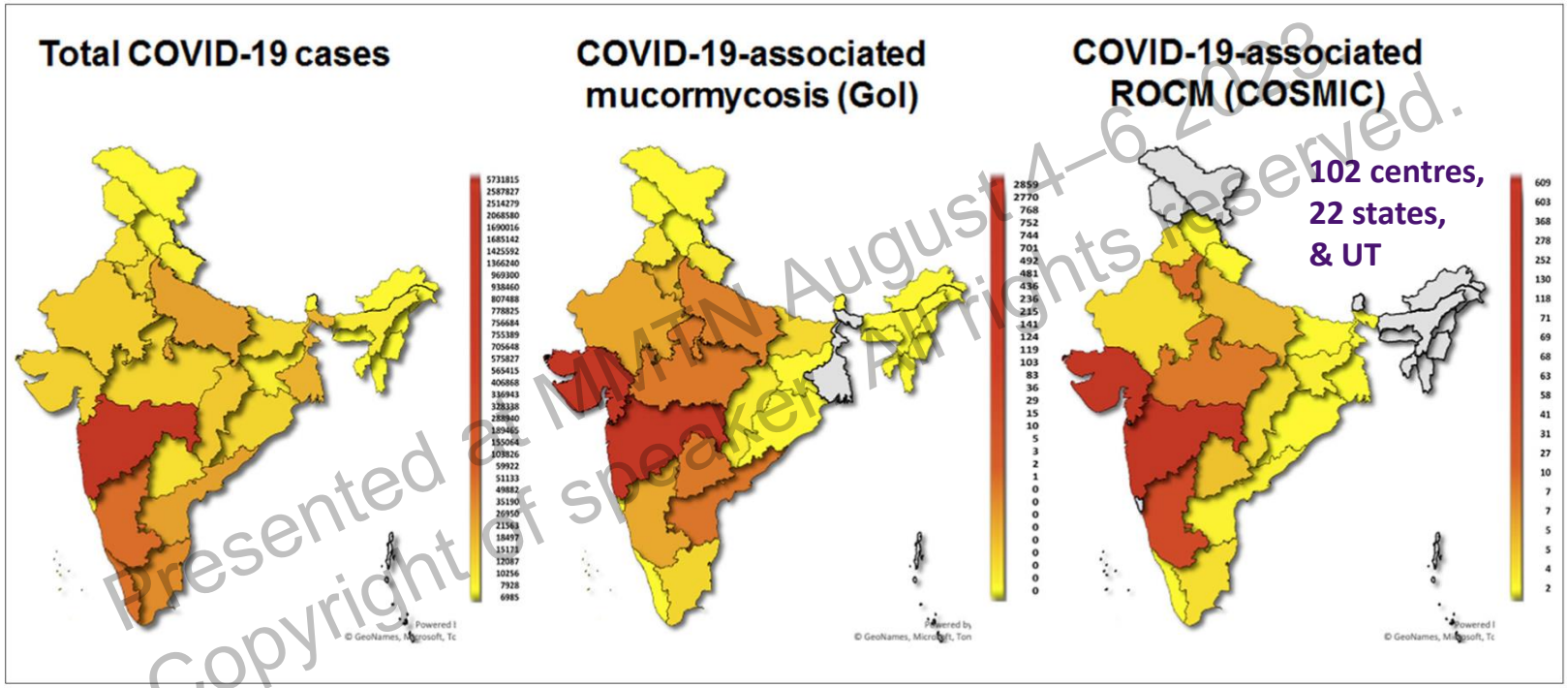
# COVID-19 Associated Mucormycosis (CAM)

- Earliest CAM was reported in March – April 2020 in a post-mortem study from UK :
- Several cases reported from many countries across the globe
- India reported two surges in CAM cases: Sept-Dec 2020 and April-July 2021
- India reported > 40, 854 CAM cases
- CAM prevalence: 0.03% (Turkey), 0.35% (Pakistan), 0.27% (India) and 0.04% (Mexico) among hospitalised COVID-19 patients;



**Bayram N *et al*. Jpn J Ophthalmol 2021, Guzman-Castro S *et al.* Mycoses 2022, Nasir N et al. Clin Microbiol Infect 2021, Patel A et al. Emerg Infect Dis 2021, Hanley B. *et al* Lancet Microbe 2020**

# State-wise distribution of COVID-19-and CAM in India (as on June 2, 2021)






Sen M. Indian J Ophthalmol 2021;69:1670-92.

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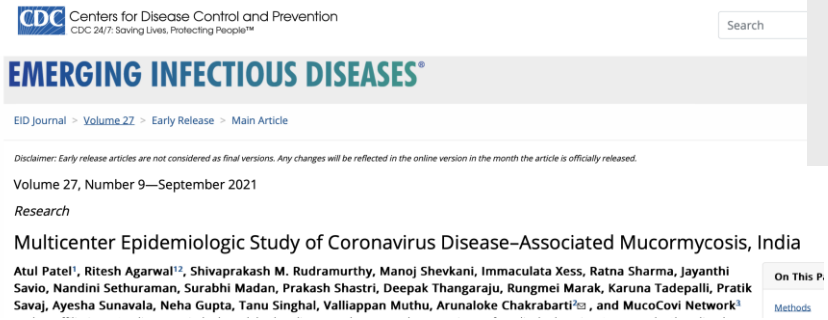
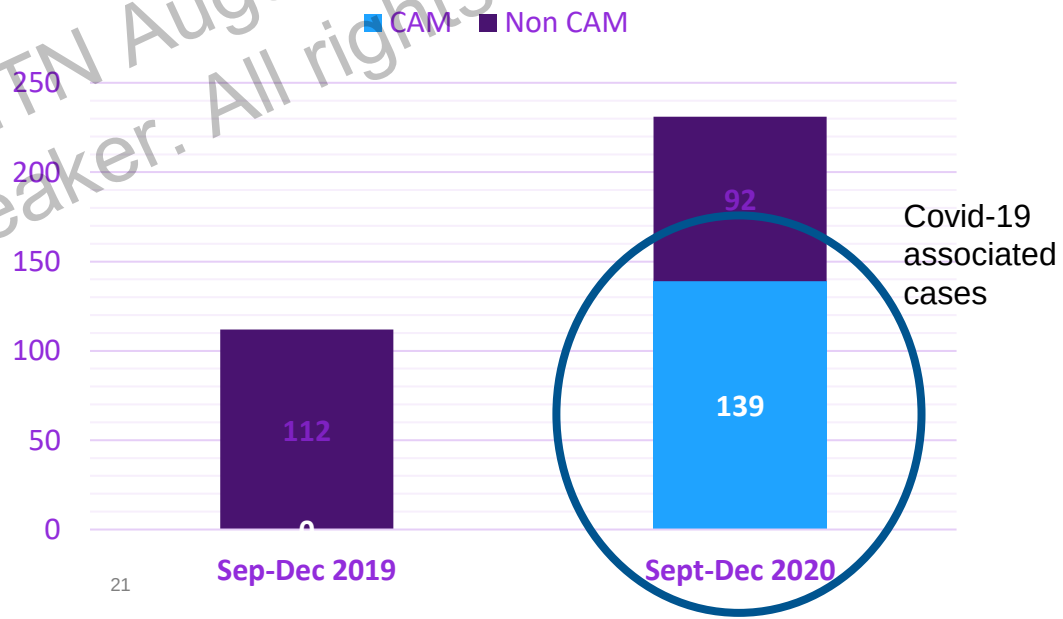



# Impact of COVID-19 on Mucormycosis in India

- Overall, CAM prevalence : 0.27%
- More mucormycosis cases were identified during the 2020 (231 cases vs 112 cases in 2019)
- The number of mucormycosis cases unrelated to COVID-19 did not differ much, indicating the increase in 2020 was chiefly attributed to Corona associated Mucormycosis

**Cumulative number of mucormycosis cases during September–December 2019 and September–December 2020 in 10 health centers, India.**








Patel A, et al.; MucoCovi Network. Multicenter epidemiologic study of coronavirus disease–associated mucormycosis, India. Emerg Infect Dis. 2021 Sep

# Multivariate analysis of risk factors for CAM

Study period: January 2021-May 2021: Single center

| | Adjusted Odd's Ratio | 95% CI | p - value |
|---|---|---|---|
| **Diabetes Mellitus** | | | <0.001 |
| **No DM** | Reference | | |
| **New DM** | **48.66** | **14.3 – 166** | **<0.001** |
| **Known case of DM** | **2.93** | **1.4 – 6.1** | **0.004** |
| **Type of Admission** | | | 0.032 |
| **Ward admission** | Reference | | |
| **ICU admission** | 0.11 | 0.03 – 0.4 | 0.002 |
| **Home Isolation** | **4.8** | **2 – 11.3** | **<0.001** |
| **Steroid Therapy** | **3.64** | **1.2 – 10.9** | **0.021** |

**Covid severity has no association with CAM**

Higher proportion of controls used tocilizumab (10.7%) as compared to cases (3%), Insignificant
OR 0.27, 95% CI (0.1-1.2).

Oxygen therapy has no relation with CAM, Higher proportion of control received oxygen



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Atul Patel et al. Medical Mycology, July 2022

# Why India has highest CAM burden

- Diabetics; New onset diabetes
- Steroids usage
- Higher environmental spore counts: Study conducted before COVID-19 pandemic and after CAM outbreak: **Biswal M, J Hosp Infect 2022, Prakash H, Med Mycol 2020**
- Seasonal variation and different spore counts in different zones of India (highest spores count in the north and south India compared to west and east Indian centre) **Biswal M, J Hosp Infect 2022 , Prakash H, Med Mycol 2020**

Received: 21 May 2022 | Revised: 11 June 2022 | Accepted: 15 June 2022

DOI: 10.1111/myc.13487

ORIGINAL ARTICLE

mycoses | WILEY

# Could cattle dung burning have contributed to the epidemic of COVID-19-associated mucormycosis in India? Results of an experimental aero-mycological study

Soundappan Kathirvel[1] | Valliappan Muthu[2] | Shivaprakash Mandya Rudramurthy[3] | Harsimran Kaur[3] | Arunaloke Chakrabarti[3] | Ritesh Agarwal[2]



TABLE 1 Growth of Mucorales in ambient air samples linked with the burning of cattle dung cakes

| | Before burning | During burning | After burning |
|---|---|---|---|
| [a]Growth of Mucorales, *n*/*N* (%) | 4/22 (18.2) | 4/22 (18.2) | [b]3/22 (13.6) |
| Species isolated | *L. corymbifera* (*n* = 3), *R. arrhizus* and *R. microsporus* (*n* = 1) | *L. corymbifera* (*n* = 2), *R. microsporus* (*n* = 1), *L. corymbifera* and *R. arrhizus* (*n* = 1) | *L. corymbifera* (*n* = 2), *R. arrhizus* (*n* = 1) |
| Average spore count, CFU/m$^3$ | $0.007\times10^3$ | $0.006\times10^3$ | $0.006\times10^3$ |

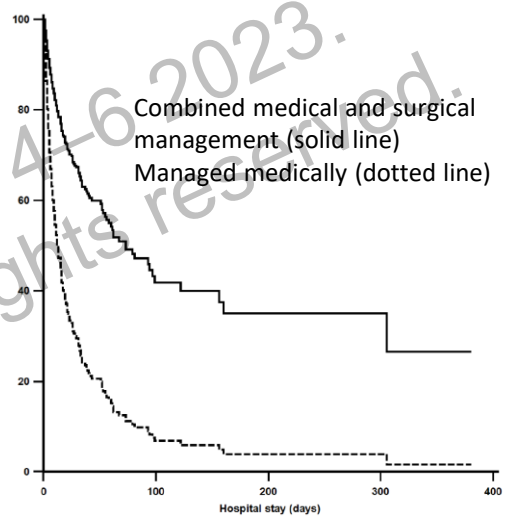
TABLE 3 Growth of Mucorales in soil samples and cattle dung (fresh and dry)

| | Growth of Mucorales *n*/*N* (%) | Species isolated | Average spore count, CFU/g |
|---|---|---|---|
| Cattle dung | | | |
| Fresh | 6/8 (75.0) | *L. corymbifera* (*n* = 5), *R. arrhizus* (*n* = 1) | $0.38\times10^4$ |
| Dry | 3/6 (50) | *L. corymbifera* (*n* = 2), *R. arrhizus* (*n* = 1) | $0.6\times10^3$ |
| Soil | | | |
| Cattle shed | 1/6 (16.7) | *L. corymbifera* (*n* = 1) | $1.5\times10^3$ |
| Common area, village | 3/3 (100) | *L. corymbifera* (*n* = 2), unidentified Mucorales (*n* = 1) | $0.6\times10^3$ |
| Common area, urban | 2/3 (66.7) | *L. corymbifera* (*n* = 1), *R. arrhizus* (*n* = 1) | $0.1\times10^4$ |

Abbreviations: CFU, colony-forming units; *L. corymbifera*, *Lichtheimia corymbifera*; *R. arrhizus*, *Rhizopus arrhizus*.

# Treatment: Challenges

- Amphotericin B: L-AmB is preferred over D-AmB
  - D-AmB is associated with higher mortality (p=0.023)






**Patel A, Clin Microbiol Infect. 2020 Jul;26(7):944.e9-944.e15**
Cornely OA, et al. Lancet Infect Dis. 2019 Dec;19(12):e405-e421

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**Methods**: Patients received short (7 to 14 days) or long (15 to 28 days) intravenous Amphotericin therapy

(Longer Rx for patients with brain involvement)

All patients received step-down posaconazole tablets, debridement, and glycemic control

The primary outcome was the treatment success at week 14, (survival and the absence of disease progression through clinical evaluation and nasal endoscopy)

**Results:** Short course (median 13 days): n=205, Treatment success 93%

Long course( 22 days): n=46, treatment success : 62%

Predictors of Mortality: Age (p= 0.027), diabetic ketoacidosis at presentation (p= 0.012), HbA1c (p= 0.019), stroke (p= 0.0001), and brain involvement (p < 0.0001)

D-AmB 52 % Short course, 67% Long Course, Lipid formulation 48% Short, 28% Long course

# Treatment challenges

- Left Hospital against medical advice: Up to ¼ of patients left hospital after receiving diagnosis of mucormycosis
- Prognosis/ Cost/ Surgical treatment / Monitoring antifungal treatment/ prolonged treatment



Patel A. *Mycoses.* 2017;1–5. Patel A, Clin Microbiol Infect. 2020 Jul;26(7):944.e9-944.e15.

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# Summary

- Asian countries (India, China) has higher case burden
- Diabetes is a leading risk factor for mucormycosis in India/ Asia
- *Rhizopus arrhizus* is commonest species isolated
- Infection with *R. microsporus* and *R. homothalicus* are increasingly reported
- Isolated renal mucormycosis in immunocompetent young male is described mainly from India and China
- Expensive and prolonged treatment for mucormycosis is a big challenge in India

# Thank you