


COVID-19-associated mucormycosis, diabetes and steroid therapy: Experience in a single centre in Western Mexico

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Abstract

Background: COVID-19-associated mucormycosis (CAM) has emerged as a challenging complication as the current pandemic has increased the population requiring treatment with corticosteroids. CAM has caused a massive outbreak in India, reported to be causing cases in Iran, Egypt and The Netherlands.

Objectives: To describe CAM cases occurring in a single centre in Western Mexico.

Methods: Our group carried out a retrospective study from May 2020 to May 2021 to identify CAM cases in patients with previous COVID-19 diagnosis.

Results: Six CAM cases occurred in a single centre in Western Mexico during the study period, most of them with diabetes ($n = 5/6$) and all received corticosteroid therapy even when only three had severe COVID-19. After analysing local COVID-19 burden, it was estimated that in this region, CAM was 300 times more frequent among COVID individuals than the estimates for general population.

Conclusion: Similar to large reports in India and other countries, CAM cases reported in this study were diagnosed in individuals with diabetes, hyperglycaemic status and with history of previous use of corticosteroids. Identifying these individuals at risk can help the early identification of CAM. In addition, strict glycaemic control and avoidance of unnecessary corticosteroid in non-severe COVID-19 cases could help in preventing this complicated fungal infection.

KEYWORDS

CAM, corticosteroids, COVID-19, diabetes, infection, mucormycosis, ROCM, SARS-CoV-2

1 | BACKGROUND

SARS-CoV-2 has caused more than 232 million infections and more than 4.5 million deaths since 2020.¹ Clinical management of severe COVID-19 includes supplementary oxygen, thromboprophylaxis, corticosteroids (specifically dexamethasone), IL-6 and JAK 1/2 inhibitors and, remdesivir.² Since the RECOVERY trial showed dexamethasone decreases mortality among severely ill COVID-19 patients³,

the population receiving corticosteroids has increased worldwide.⁴ World Health Organisation (WHO) has recommended from a public health point of view, to administrate dexamethasone and/or other steroids only in severe cases and at the dose where evidence has shown to have a benefit and discourages the use as preventive medication or its use in non-severe cases.⁴ COVID-19-associated fungal infections have emerged as a challenging complication especially among severely ill individuals mostly previously treated with

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immunosuppressive agents. Mucormycosis is one of these COVID-19-associated fungal infections that has caused a massive outbreak in India with up to 28,000 cases in less than a year.^{5,6} Increasing incidence of CAM cases has been also reported in Iran, The Netherlands and, Egypt.⁷⁻⁹ Uncontrolled diabetes and newly diagnosed diabetes are main risk factor for CAM.¹⁰ Inappropriate use of steroids in CAM individuals has estimated to be up to 63% and their use has been also identified as an independent risk factor for CAM.^{5,10} To contribute to the evidence about the epidemiology and characteristics of this infection, we report six cases of COVID-19-associated mucormycosis (CAM) in a single reference mycology Centre in Western Mexico.

2 | METHODS

Since 2019, our group established a mycology reference laboratory and multidisciplinary team in the Hospital General 'Dr Miguel Silva' SSM, Morelia, Michoacan, Mexico (Western Mexico). Since then, the number of identified fungal infections has duplicated. The team involved in the identification of fungal infections includes two infectious diseases specialists, three clinical microbiologists, two surgeons, one neurologist and one pathologist.

Among COVID-19-associated fungal infections attended by our team, we conducted a retrospective search from May 2020 to May 2021 to collect clinical data from CAM cases diagnosed at the centre. Informed consent was obtained retrospectively from the patient or a family member to publish information and images. Project was approved by local Institutional Review Board with number 575/01/21. A proven CAM case was defined in individuals with history of proven COVID-19 (compatible clinical data and positive SARS-CoV-2 RT-PCR assays carried out at local government reference laboratory) and compatible clinical, endoscopic and imaging features plus positive mycological evidence of mucormycosis on tissue or sterile fluid (broad aseptate hyaline hyphae) by direct microscopy using 10% KOH preparation and/or isolation of Mucorales. Fungus grown on culture were identified by MALDI-TOF. A probable CAM case was defined as individuals with history of proven COVID-19 and compatible clinical, endoscopic and imaging features of mucormycosis.^{5,6}

3 | RESULTS

Six CAM cases were identified. All cases occurred between December 2020 and May 2021. During this 5-month period, 14,435 COVID-19 cases were reported in Morelia by the local ministry of health¹¹ representing 0.4 CAM cases per 1000 COVID-19 cases. Median age was 52 years old (IQR 45–57). Five of the six individuals had diabetes mellitus of which, two had ketoacidosis at the time of CAM. Three cases had diabetes diagnosed 15 years ago, one case 2 years ago and one was diagnosed with diabetes at the same time as CAM. Glycated haemoglobin was available for three of the five cases and were above 8% (8.4%, 10.5%, 11.3%). Four of six cases did not required hospital manage for COVID-19 and were followed up

ambulatory. The five cases in diabetic individuals were rhino-orbital-cerebral mucormycosis (ROCM). CAM was diagnosed after a median of 15 days (IQR = 8–21) from COVID-19 diagnosis and all six of them received corticosteroid as adjuvant therapy (median 8 days, IQR 7–10). Five cases received dexamethasone, and two received dexamethasone plus a different corticosteroid. Patients received a median cumulated dose of steroid in prednisone equivalent of 400 mg (IQR 280–496 mg), Table 1. Four cases were initially diagnosed by direct microscopy, four had positive culture and were identified by MALDI-TOF as *Mucor circinelloides* (3/4) and *Rhizopus puiculus* (1/4), Table 1 and Figure 1. Five cases were proven and, only one was considered probable as the patient died before any further diagnostic approach could be done.

ROCM cases were characterised by orbital oedema (5/5), palate necrotic ulcer (4/5), facial oedema and pain (4/5), orbital necrosis and ecchymosis (2/5), proptosis (3/5), blindness and endophthalmitis (3/5), headache (3/5), dyspnoea (1/5), subcutaneous emphysema (1/5), Figure 2. Major findings at imaging were: Pansinusitis, sinus bone erosion, periorbital oedema, subcutaneous gas, and hypodense cerebral areas, Figure 3. The sixth CAM case was in a non-diabetic individual, and it was the only female and was diagnosed in lungs as part of an extensive diagnostic approach (bronchioalveolar lavage and respiratory cultures) due to progressive ARDS due SARS-CoV-2.

All ROCM cases were treated with amphotericin B deoxycholate (AMBD) at a dose of 1 mg/kg/day, and the pulmonary CAM with liposomal amphotericin B at a dose of 5 mg/kg/day. Surgery was carried out in two ROCM cases. Five of six individuals died, Table 1.

4 | DISCUSSION

We reported six CAM cases in patients previously receiving corticosteroids, five of which had diabetes. Even before COVID-19 pandemic, ROCM cases were mainly diagnosed among individuals with uncontrolled diabetes in Mexico.¹² The pre-COVID-19 estimated burden of mucormycosis for Mexico is 0.12/100K population.¹³ In the current report, mucormycosis occurred 300 times more frequently among COVID-19 individuals. This estimate has the limitation of only considering cases occurring at the current local hospital (the biggest in Morelia city); hence, frequency is most probably underestimated. However, this estimate highlights how frequent this fungal infection is among COVID-19 managed in this area. Dexamethasone, a long-acting corticosteroid, leads to hyperglycaemia by increasing insulin resistance, gluconeogenesis and, less peripheral glucose uptake.¹⁴ Corticosteroids can induce diabetes in the same individuals at risk of severe COVID-19 such as elderly, family history of diabetes, obesity.¹⁴ By itself, hyperglycaemia increases the releasing of reactive oxygen species and pro-inflammatory cytokines, it also affects phagocytosis and intracellular fungal killing.¹⁵ In addition, hyperglycaemia favours Mucorales to bind endothelial cells by increasing the expression of GRP78 (a member of the HSP70 protein family expressed in endoplasmic reticulum [ER] of cells) which is known to be the human

TABLE 1 Clinical characteristics of six COVID-19-associated mucormycosis (CAM) cases in Western Mexico

Case	1	2	3	4	5	6
Gender	Male	Male	Male	Male	Female	Male
Age	65	62	36	56	49	48
Diabetes	Yes	Yes	Yes	No	Yes	Yes
HbA1c (%)	10.5	11.3	^b	^b	—	8.4
Characteristics before CAM						
SatO ₂ at the time of COVID-19	85%	94%	95%	95%	95%	82%
Pa/FiO ₂ or SatO ₂ /FiO ₂ at the time of COVID-19 diagnosis	404	447	451	451	200 ^a	70
ARDS	No	No	No	No	Yes	Yes
Required oxygen during COVID-19	Yes, at home	No	No	No	IMV	IMV
Other co-infections	No	No	No	No	No	No
Previous antibiotics	Amoxi/clav	No	No	No	CZA, Doxi	Lev, CRO, Mero
Characteristics of CAM						
COVID-19 to CAM (days)	21	21	21	7	8	10
Site of infection	ROCM	ROCM	ROCM	ROCM	Lung	ROCM
Diagnostic tool						
Direct microscopy (+)	KOH	KOH	No	No	KOH	KOH
Culture	No	Yes	—	Yes	Yes	Yes
Fungal species		<i>M. circinelloides</i>		<i>M. circinelloides</i>	<i>R. pucilus</i>	<i>M. circinelloides</i>
Corticosteroid use	DEXA PDN	PDN	DEXA	MPDN, DEXA	DEXA	DEXA
Cumulated steroid dose (prednisone equivalent)	500 mg	400 mg	400 mg	785 mg	280 mg	280 mg
Time on steroid treatment (days)	10	10	10	7	7	7
Ketoacidosis at CAM	No	No	Yes	No	—	Yes
Tests at CAM diagnosis						
WBC	11,900	17,800	15,000	15,900	13,200	23,200
Haemoglobin	14.2	14.9	15.3	11.1	16.1	10.1
Neutrophils	—	88%	89%	94%	90%	89%
Lymphocytes	—	7%	5%	5%	7%	6%
Platelets	—	162,000	240,000	112,000	28,000	239,000
C-reactive protein	—	93.7	—	27.9	6.37	515
LDH	—	576	—	—	311	799
Treatment	AMBD	AMBD+surgery	AMBD	AMBD+surgery	LAMB	AMBD
Outcome	Died	Alive	Died	Died	Died	Died

Abbreviations: AMBD, amphotericin B deoxycholate; Amoxi/clav, amoxicillin/clavulanate; ARDS, acute respiratory distress syndrome; CRO, ceftriaxone; CZA, ceftazidime; DEXA, dexamethasone; Doxi, doxycycline; HbA1c, glycated haemoglobin; IMV, invasive mechanical ventilation; LAMB, liposomal amphotericin; Lev, levofloxacin; Mero, meropenem; MPDN, methylprednisolone; PDN, prednisone; ROCM, rhino-orbital-cerebral mucormycosis; SatO₂, arterial oxygen saturation by oximetry.

^aOn the day of diagnosis, patient had a ratio = 306, 24 h after ratio was 200 and required invasive mechanical ventilation.

^bDied before having a sample.

receptor for these fungi in endothelial cells.¹⁶ Hypotheses on what is the role of SARS-CoV-2 in the pathogenesis of mucormycosis have been proposed recently. One of these proposed mechanisms

is that GRP78 acts as a co-receptor for the receptor-binding domain of SARS-CoV-2 allowing the virus to entry and infect cells.¹⁷ Once inside the cells, SARS-CoV-2 proteins would trigger unfolded

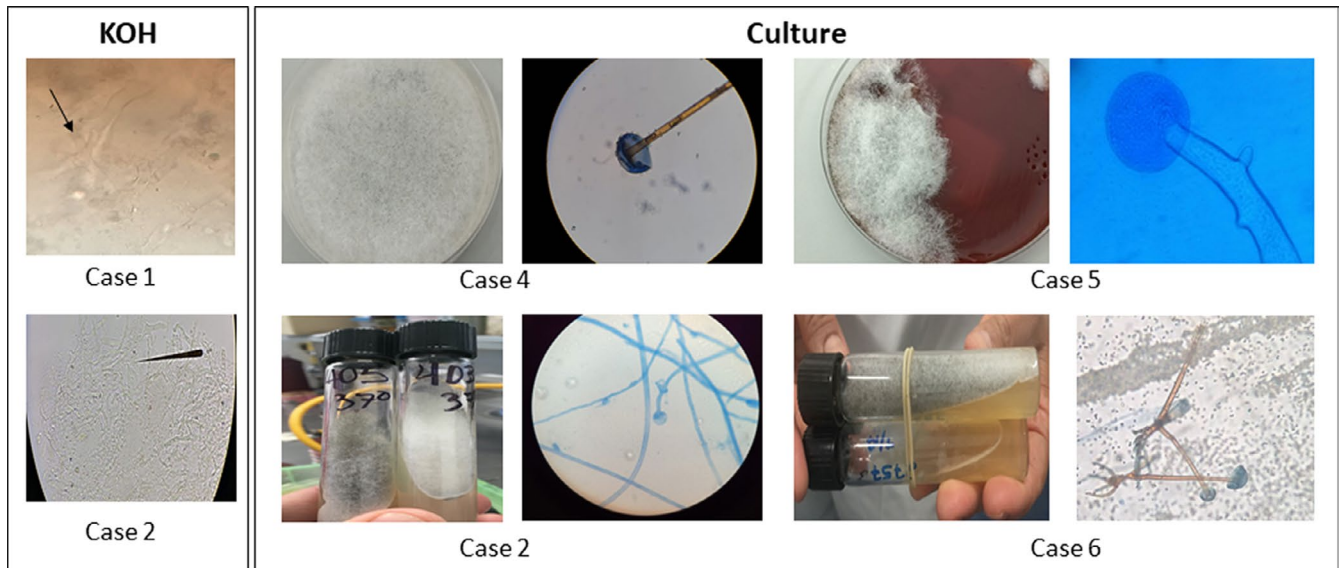


FIGURE 1 KOH and culture from CAM cases. Four cases were initially diagnosed by direct microscopy. Case 1 was diagnosed only by KOH cytology. Four cases had positive culture, cases 2, 4, 5, 6



FIGURE 2 Clinical characteristics of patients with COVID-19-associated rhino-orbital-cerebral mucormycosis. Case 1: Male 65 YO, diabetes. Clinical features: oedema, necrosis in left orbit and an ulcer in palate but rapidly progressed over the next 2 days to subcutaneous emphysema, proptosis, and endophthalmitis. Case 2: 62 YO male, Diabetes and recently diagnosed with hepatic cirrhosis. Clinical manifestations were headache, left-side facial pain, proptosis, orbital and palate oedema. Palate also showed a necrotic ulcer. Case 4: 56 YO male, diabetes. Clinically, headache, and left eye pain and oedema. Left eye with blindness, ptosis, and proptosis. A necrotic palate ulcer was also seen. Case 6: Male, 48 YO with 15-year diabetes. After 5 days in hospital due to severe SARS-CoV-2 and ketoacidosis, patient showed bilateral orbit oedema, ecchymosis, and purulent secretion

protein response at ER leading to higher expression and levels of GRP78 as seen in COVID-19 pneumonia patients.¹⁸ Another proposed mechanism is the potential of SARS-CoV-2 of producing acute diabetes and hyperglycaemia as it damages and triggers apoptosis of pancreatic β cells in COVID-19 severely ill individuals.¹⁹ All these mechanisms would perpetuate a cycle where the adequate environment for mucormycosis is favoured. In a study from India where 2826 CAM cases were reported, 87% of these cases received corticosteroids and 21% for more than 10 days.⁶

Using corticosteroids for longer than 10 days is not the current recommendation of use in COVID-19 severe patients.^{1,3} This means that in this report, at least 500 individuals received a higher dose of corticosteroids. This is particularly important as in a case-control study, Bhanuprasad et al showed that diabetes mellitus and the use of corticosteroid increased the risk of CAM by 4 and 28 times, respectively. Of importance to highlight, in Bhanuprasad et al¹⁰ report most of corticosteroid use was unnecessary as most COVID-19 cases were non-severe.

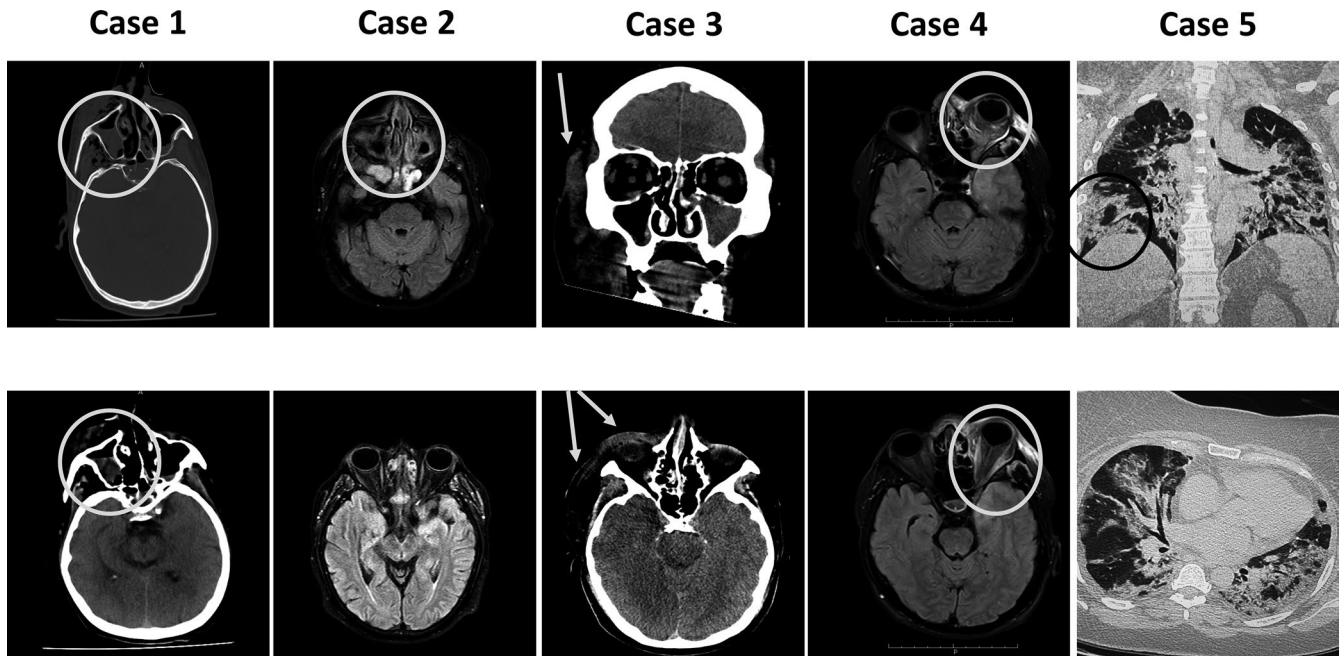


FIGURE 3 Findings in imaging in patients with CAM. Case 1. CT scan showing pansinusitis, maxillar bone erosion, subcutaneous and intramuscular dissecting gas (white circle), Case 2. CT scan with mucosal thickening at in maxillary and ethmoid sinuses with communication between sinuses and cranial cavity. Case 3. CT scan showing pansinusitis, bone erosion, periorbital and hemi-facial oedema (white arrow), subcutaneous gas, hypodensity in frontal lobes. Case 4. MRI showing left eye proptosis (white circle), postgadolinium enhancing of pre- and periorbital muscles and soft tissues. Sinus thickening and soft tissue dissection. Case 5. Wide bilateral consolidations, air bronchogram, image compatible with reversed halo sign (black circle)

The identification of individuals at risk, strict glycaemic control and avoidance of unnecessary corticosteroid in non-severe COVID-19 cases (normal oxygen saturation on room air) can help in preventing this complication. To save individuals from unnecessary deaths, improving local diagnostic capacities and formation of multidisciplinary teams are essential in providing early diagnosis and treatment.²⁰

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CONFLICT OF INTEREST

Authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Salvador Guzmán Castro: Data curation (equal); Investigation (equal); Writing-review & editing (equal). Luis David Chora-Hernandez: Conceptualization (equal); Data curation (equal); Investigation (lead); Supervision (lead); Writing-review & editing (equal). Antonio Sánchez Rangel: Data curation (equal); Writing-review & editing (equal). Gersain Trujillo Alonso: Methodology (equal); Writing-review & editing (equal). Ivan Calvo Villalobos: Investigation (equal); Writing-review & editing (equal). Edgar Ferrer Alpuin: Data curation (equal); Writing-review & editing (equal). Miguel Ruíz Jimenez: Data curation (equal); Formal analysis (equal). Dora E E. Corzo-Leon : Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Writing-original draft (lead).

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REFERENCES

1. World Health Organization. WHO Coronavirus (COVID-19) dashboard. Accessed September 29, 2021. <https://covid19.who.int/>
2. COVID-19 Treatment Guidelines Panel. *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*. National Institutes of Health. Accessed March 03, 2021. <https://www.covid19treatmentguidelines.nih.gov/>
3. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704.
4. Fernandes M, Brábek J. COVID-19, corticosteroids and public health: a reappraisal. *Public Health*. 2021;197:48-55.
5. Rudramurthy SM, Hoenigl M, Meis JF, et al. ECMM/ISHAM recommendations for clinical management of COVID-19 associated mucormycosis in low- and middle-income countries. *Mycoses*. 2021;64(9):1028-1037.
6. Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U; members of the Collaborative OPAL-IJO Study on Mucormycosis in COVID-19 (COSMIC) Study Group. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India – Collaborative OPAL-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. *Indian J Ophthalmol*. 2021;69(7):1670-1692.
7. Avatef Fazeli M, Rezaei L, Javadirad E, et al. Increased incidence of rhino-orbital mucormycosis in an educational therapeutic hospital during the COVID-19 pandemic in western Iran: an observational study. *Mycoses*. 2021;64(11):1366-1377.
8. Buil JB, van Zanten ARH, Bentvelsen RG, et al. Case series of four secondary mucormycosis infections in COVID-19 patients,

- the Netherlands. *Eurosurveillance*. 2021;26(23):doi:10.2807/1560-7917.ES.2021.26.23.2100510
9. Fouad YA, Abdelaziz TT, Askoura A, et al. Spike in rhino-orbital-cerebral mucormycosis cases presenting to a tertiary care center during the COVID-19 pandemic. *Front Med (Lausanne)*. 2021;8:doi:10.3389/fmed.2021.645270
 10. Bhanuprasad K, Manesh A, Devasagayam E, et al. Risk factors associated with the mucormycosis epidemic during the COVID-19 pandemic. *Int J Infect Dis*. 2021;111:267-270.
 11. Secretaria de salud Michoacan. Centro Estatal de Operaciones COVID-19, SSM. Información por Municipio: Morelia. (Consulted on 2021 June 23). <https://covid19.srs.care/#/michoacan>
 12. Corzo-León DE, Chora-Hernández LD, Rodríguez-Zulueta AP, Walsh TJ. Diabetes mellitus as the major risk factor for mucormycosis in Mexico: epidemiology, diagnosis, and outcomes of reported cases. *Med Mycol*. 2018;56(1):29-43.
 13. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. *J Fungi (Basel)*. 2019;5(1):26.
 14. Alessi J, de Oliveira GB, Schaan BD, Telo GH. Dexamethasone in the era of COVID-19: friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes. *Diabetol Metab Syndr*. 2020;12:80.
 15. Morales-Franco B, Nava-Villalba M, Medina-Guerrero EO, et al. Host-pathogen molecular factors contribute to the pathogenesis of *Rhizopus* spp. in diabetes mellitus. *Curr Trop Med Rep*. 2021;8(1):6-17.
 16. Liu M, Spellberg B, Phan QT, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. *J Clin Investig*. 2010;120(6):1914-1924.
 17. Carlos AJ, Ha DP, Yeh D-W, et al. The chaperone GRP78 is a host auxiliary factor for SARS-CoV-2 and GRP78 depleting antibody blocks viral entry and infection. *J Biol Chem*. 2021;296:100759.
 18. Sabirli R, Koseler A, Goren T, Turkcuer I, Kurt O. High GRP78 levels in Covid-19 infection: a case-control study. *Life Sci*. 2021;265:118781.
 19. Wu C-T, Lidsky PV, Xiao Y, et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. *Cell Metab*. 2021;33(8):1565-1576.e5.
 20. Rodriguez Tudela JL, Cole DC, Ravasi G, et al. Integration of fungal diseases into health systems in Latin America. *Lancet Infect Dis*. 2020;20(8):890-892.

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