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COVID-19 AND FUNGAL INFECTIONS (RPL KODIYANPLAKKAL, SECTION EDITOR)

Endemic Mycoses and COVID-19: a Review

Fernando A. Messina[1] · **Gustavo Giusiano**[2] · **Gabriela Santiso**[1]

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Abstract

Purpose of Review SARS-CoV-2 generates an atypical pneumonia with high morbidity and mortality. In many cases, the torpid evolution was related to bacterial or fungal co-infections. Non-specific manifestations of COVID-19 infection can make the differential diagnosis with other systemic diseases even more difficult. A review of systemic endemic mycoses associated with COVID-19 was carried out. We will describe epidemiological data, clinical characteristics of the endemic mycosis, and different diagnostic resources.

Recent Findings Database search process in PubMed, Latindex, and other online web was performed. From 78 published cases, coccidioidomycosis was the most frequent association followed in second place by histoplasmosis. Highly variable diagnostic methodologies were used, but all were useful.

Summary Mortality caused by these endemic mycoses does not seem to have been modified by COVID-19.

Keywords COVID-19 · Fungal infection · Endemic mycoses · Co-infection

Introduction

Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, in December 2019 [1]. SARS-CoV-2 is the COVID-19 etiological agent. Being a highly contagious microorganism, it spread rapidly and generated one of the most relevant pandemics in recent years, declared on March 11, 2020, by the World Health Organization (WHO) [2].

The most commonly affected organ is the lung, and therefore the main clinical manifestations of COVID-19 are respiratory signs, including cough, dyspnea, sore throat, and fever [3]. In severe states of COVID-19, the development of pneumonia with acute respiratory distress syndrome (ARDS), respiratory failure, and/or death has occurred [4].

Prolonged hospitalization was very frequently required in patients with comorbidities such as obesity, cardiovascular disease, and chronic respiratory pathologies. Moreover, the multiple treatments applied generated complications such as nosocomial bacterial infections and candidemia [5]. On the other hand, in regions with a high prevalence of metabolic diseases such as diabetes, COVID-19-associated mucormycosis was associated with high morbidity and mortality [6].

Likewise, it is also important to highlight that the cosmopolitan fungal diseases with a special tropism for a damaged lung, such as aspergillosis, were also a widely discussed topic. Meanwhile, endemic mycoses were not initially a focus of study in relation to this pandemic.

Endemic Mycoses

Systemic endemic mycoses (EM) share certain characteristics:

1. They occur in geographical areas with a specific soil and climate.
2. They are caused by a diverse group of dimorphic fungi.
3. In most cases, they are acquired by inhalation, with the respiratory system being the first target of infection. Cases of secondary reactivation are often seen.

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✉ Fernando A. Messina
fmessina35@gmail.com

[1] Mycology Unit, Francisco Javier Muñiz Infectious Diseases Hospital, Buenos Aires, Argentina

[2] Mycology Department, Instituto de Medicina Regional, Universidad Nacional del Nordeste, Consejo Nacional de Investigaciones Científicas Y Técnicas (CONICET), Resistencia, Argentina

4. They can cause disease in both immunosuppressed and immunocompetent hosts.

The etiological agents related to this group of mycoses are species of the genera *Histoplasma*, *Paracoccidioides, Coccidioides*, *Blastomyces*, *Talaromyces*, and *Emergomyces*.

EM are well known to cause systemic and focal disease restricted to geographic areas of known endemicity. Nevertheless, in recent decades, reports of endemic fungal infections in areas previously considered to be "non-endemic" have been published with increasing frequency. Ecological variations such as consequences of climatic and anthropogenic changes, migration, the increased use of immunosuppressants, improvements in diagnostic techniques, and clinical recognition are possible causes for these changes. Bearing this in mind, some authors affirm that it is probable that we are facing an evolution of the concepts that previously defined the endemic regions of these mycotic diseases [7•].

Diagnosis of Systemic Endemic Mycoses

Several testing options are available for diagnosis of these mycoses, including microscopy, culture, specific antigen and antibody detection, and molecular methods [8••]. The issue is that specific tests are not available for the diagnosis of all EM, or they are not available in all countries included in endemic areas. Table 1 shows conventional, molecular, immunological diagnostic methods for the different EM.

Systemic Endemic Mycoses–COVID-19 Association

Using PubMed, Latindex, Google Scholar, Scopus, and SciELO databases, a review on the co-infection between systemic endemic mycoses with COVID-19 was carried out.

Until December 31, 2021, seventy-eight cases of COVID-19 associated with EM were published. The geographical distribution of these cases is shown in Fig. 1. Clinical, microbiological data and evolution of these published cases are presented in Table 2.

Coccidioidomycosis

Coccidioidomycosis (CM) is a fungal infection of the arid and semi-arid regions of the American continent. It is caused by two epidemiologically and genetically diverse species, *Coccidioides immitis* and *Coccidioides posadasii*. To date, both species are believed to be phenotypically similar in terms of clinical manifestations, in vitro susceptibility, and response to antifungal therapies. Genotypic variation between fungal species could contribute to differences in virulence [13].

The endemic area for *C. immitis* encompasses primarily the Central Valley of California, but additional endemic foci such us north and eastern Washington State were documented. *C. posadasii* is found in desert areas of Arizona, Texas, Utah, and Mexico, as well as in Central America, the Comayagua Valley of Honduras, and the Montague Valley of Guatemala. In South America, CM was reported in northeastern Colombia; Zulia, Lara, and Falcón states in Venezuela; Tucumán, Catamarca, Santiago del Estero, Neuquén, and Río Negro provinces of Argentina; and Piaui, Maranhao, Ceara, and Bahia states in Brazil [7•].

CM and COVID-19 co-infection are unavoidable, and a variety of clinical scenarios are possible. After an initial *Coccidioides* infection resolves, the fungus can remain dormant in the lungs and reactivate under certain conditions. It has been postulated that the COVID-19 pandemic could not only affect the CM presentation but also reactivate the disease in a patient with CM whose disease has progressed to a chronic but quiescent state [14, 15••].

The most likely case would be a person with pulmonary CM who subsequently develops COVID-19. It should be noted that symptoms of these two diseases are remarkably similar and include fever, dry cough, dyspnea, myalgia, and headache. Radiological changes can also mimic each other.

SARS-CoV-2 can also complicate patients with prolonged disseminated disease or primary infection with persistent inflammation. CM patients with suppressed immune responses, such as patients with hematologic malignancies, HIV, and organ transplants, are also at increased risk of disseminated disease.

Cases of co-infection COVID-19 in patients with CM are presented in Table 2.

Histoplasmosis

It is the most frequent endemic mycosis in the world and the only one with cases reported in the five continents [7•]. The endemic area of this mycosis is expanding, especially in China and South America [16].

Related to the inhaled fungal load and the host's immune system, it can be observed from an asymptomatic infection to severe pneumonia [17]. In immunocompromised patients, disseminated forms with compromise of the reticuloendothelial system are observed [18]. In South America, cutaneous and mucocutaneous lesions are observed in a high percentage of histoplasmosis cases [18]. Fortunately, intestinal or central nervous system involvement seems to be rare, but must be diagnosed quickly because they are serious clinical conditions.

Different methodologies are used for the diagnosis. The performance of the different tests will vary depending on the

Table 1 Methods for diagnosis of systemic endemic mycoses

Mycoses	Direct exam fresh/stain	Culture	Antibody detection	Specific antigen detection	Molecular methods
Paracoccidioidomycosis [9]	Wet mounts + + + +	Low sensitivity Increasing with samples from sterile sites	ID, CIE, PFC	Not available	Diagnosis in biological materials * In house methods not routinely available
	Giemsa + +	(1–4 weeks)	Diagnosis and prognosis		Species identification: sequencing
	(Variable — sample dependent)	Blood culture: Low performance	(S: 70–100%)		
Histoplasmosis [10]	Giemsa + + + +	Gold standard + + + + (2–3 weeks)	Chronic forms ID, CIE, PFC, ELISA + + + +	In immunocompromised	Diagnosis in biological materials *. Not standardized Not routinely available
		Blood culture High performance in HIV	Low performance acute subacute forms	Galactomannan in urine/serum ELISA—LFA	Species identification: sequencing
				(S: 80%; E: 90%)	
Coccidioidomycosis [8••]	Wet mounts + + +	2–3 weeks	Acute forms AL, chronic forms ID, CIE, PFC, ELISA, and LFA	In immunocompromised	Diagnosis in biological materials *. Not standardized Not routinely available
	Giemsa + +	Blood culture: low performance		Galactomannan in urine/serum (S: 75%)	Species identification: sequencing
Blastomycosis [10]	Wet mounts + + / + + +	Most sensitive than direct exam + + +	ID—S: 65–80%	Enzyme immunoassay (to test urine, serum, BAL, and CSF)	Diagnosis in biological materials*
	Giemsa + +	(2–6 weeks)	ELISA targeting the BAD-1 (S: 88%)		Not standardized Not routinely available
	Variable — sample dependent	Blood culture: no			
Talaromycosis [11•]	Giemsa + + +	Bone marrow (100%), skin (90%), and blood (70%)	Recombinant Mp1p antigen by ELISA 4D1 monoclonal antibody against the yeast phase in an inhibitory-EIA and an immunochromatographic test		Diagnosis in biological materials*: Real time PCR Species identification: sequencing
			S: 88%; VPP 100%; VPN 96%		
Emergomycosis [12]	Giemsa + + +	Blood, skin tissue, bone marrow, lymph node, BAL	Not available		Species identification: sequencing

PCR polymerase chain reaction

*Biological materials: sputum, BAL, biopsy, punctions, blood; ID: immunodiffusion; PFC: complement-fixation; CIE: counter immune-electrophoresis; ELISA: enzyme-linked immunosorbent assay; LFA: lateral flow assay

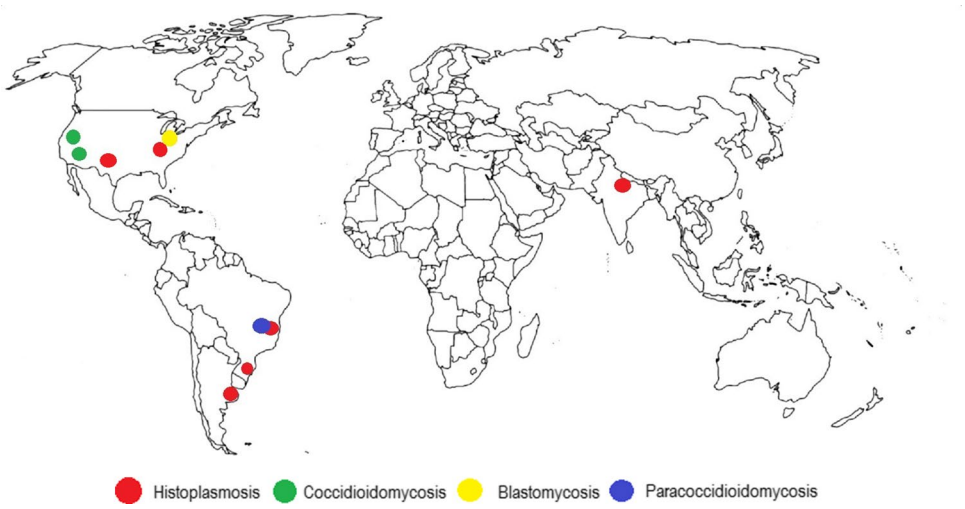

Fig. 1 Geographical areas in which EM-COVID 19 cases were informed

response of the host [19]. Histoplasmosis (HC) is one of the most frequent opportunistic diseases in people living with HIV. For this reason, it should be included among the differential diagnoses in patients with low CD4 T lymphocytes, suffering or not COVID-19. But it is noteworthy that in this review most of patients with COVID-19 and histoplasmosis were HIV negative.

Reported cases about histoplasmosis co-infection with COVID-19 are described in Table 2.

Emergomycosis

Emergomycoses are systemic EM produced by dimorphic fungi of the genus *Emergomyces*. Cases of this disease have been detected in Asia, Africa, Europe, and North America. Most of these cases are diagnosed in Africa. They are frequently seen in immunocompromised patients, especially advanced HIV disease. The lungs are the entry point of the infection, and the infecting element is the microconidia of the mycelial phase. Conversion of these conidia into their yeast phase (parasitic form) occurs, and if the host cannot control the infection, it spreads through the blood to various organs, such as the skin, liver, spleen, lymph nodes, and bone marrow [12].

Skin and mucous membrane biopsy, bronchoalveolar lavage, blood cultures by lysis-centrifugation, and lymph node biopsies or punctures are the most studied clinical samples for mycological examination. Although the global emergence of emergomycosis has recently been considered, no cases associated with COVID-19 have been yet reported.

Talaromycosis

Talaromycosis is an invasive mycosis caused by the thermally dimorphic saprophytic fungus *Talaromyces marneffei* endemic in Asia. This mycosis occurs predominantly in immunocompromised. The lungs are the primary portal of entry.

Talaromycosis is estimated to have a pooled prevalence of 3.6% (range 0.13–19.63%) in people living with HIV/AIDS, with the greatest risk of infection in people with a CD4 cell count < 200 cells/mm^3 [20]. In non-HIV-infected individuals, talaromycosis has been increasingly described in patients with other immunosuppressing conditions, such us primary immunodeficiencies, autoimmune diseases, malignancies, and iatrogenic immunosuppression [21].

To date, there are no reports of co-infection COVID-19 and talaromycosis.

Blastomycosis

The geographic region where blastomycosis (BM) is considered endemic include areas surrounding the Great Lakes and the river basins of the Ohio, Mississippi, and St. Lawrence rivers, including many US states and provinces of Canada. Northwestern Ontario and north-central Wisconsin are defined as hyperendemic areas [22].

In the USA, similar rates of testing for blastomycosis and other systemic endemic fungal infections before and during the COVID-19 pandemic was reported. Although blastomycosis was not considered underdiagnosed in the context of the pandemic in this US national survey, no published reports of blastomycosis have been found so far [23].

Although a relationship between SARS-CoV-2 and *Blastomyces* has not been observed, some cases of co-infection have occurred but have not been informed [24]. Only a case of pulmonary blastomycosis reactivation in COVID-19 acute respiratory distress syndrome in a young post-partum female, who recovered with extensive post infection lung damage, was presented [25]. The case is described in Table 2.

Table 2 Cases of endemic mycosis associated with COVID-19 infection

Etiological agent Author	Country	Cases	Sex/age	Underlying risk factors	Diagnosis	Clinical manifestations	Initial treatment	Outcome
CM Huff D [15••]	USA	60 having coccidioidomycosis either prior, concurrently, or within 6 weeks after COVID-19 infection	37 M/56 (range 17–82)	20: Immunosuppressive therapy 13: Solid organ transplant, 22: Dexamethasone	Serology others not clarified	54: lungs 3: positive antibody test in HIC 2: MNG 1: disseminate no MNG	FCZ (IVZ in one case)	Alive
CM Krauth D S [30]	USA	1	M/23	SARS-CoV-2-mediated immunosuppression	Skin biopsies	Generalized lymphadenopathy	AMB—L	Alive
CM Nassif E F [31]	USA	1	F/67	Asthma and asbestosis LIPOSARCOMA	Biopsies	Pulmonary nodules, a chest wall mass and bone lesions	FCZ	Alive
CM Chang, C.C [32]	USA	1	F/48	Heart failure	IgM and IgG by IDA and CF titers of 1:2	Atypical pneumonia	FCZ	Alive
CM Shah, A.S [33]	USA	1	M/48	Uncontrolled DM	Serology and CF titers of 1:32	Lungs	ND	Alive
CM Chen J C [34]	USA	1	M/65	Uncontrolled DM	Skin biopsies and CSF	Lungs, cutaneous lesions and MNG	AMB—L	Death
HC Messina F [35]	ARG	1	F/36	HIV	Urinary antigen, direct exam expectoration	Lung, skin	AMB—Dc	Alive
HC Messina F [5]	ARG	1	M/29	HIV	Urinary antigen, serology, nested PCR	Gastrointestinal involvement	AMB—CL	Alive
HC Basso RP [36]	Brazil	1	F/43	HIV	Urinary antigen, direct exam expectoration	Lung, liver, spleen	ITZ	Unknown
HC de Macedo PM [37]	Brazil	1	M/20	No comorbidities	Serology, sputum nested PCR	Lung	ITZ	Alive
HC de Macedo PM [37]	Brazil	1	M/32	No comorbidities	Urinary antigen, sputum nested PCR	Lung	ITZ	Alive
HC Bertolini M [38]	ARG	1	M/43	HIV	Scarification	Lung, skin	AMB	Alive
HC Maldonado I [39]	ARG	1	M/57	Renal transplant	Oral mucosa biopsies, urinary antigen	Lung, skin, oral mucosa	AMB—ITZ	Alive

Table 2 (continued)

Etiological agent Author	Country	Cases	Sex/age	Underlying risk factors	Diagnosis	Clinical manifestations	Initial treatment	Outcome
HC Stasiak CES [40]	Brazil	1	F/37	No comorbidities	Serology	Lung	ITZ	Alive
HC Taylor M [41]	USA	1	M/50	Asthma	Urinary antigen, histopathology lung biopsy	Lung, hepatosplenomegaly	AMB—L	Alive
HC Khanna A [42]	India	1	F/65	Chronic liver disease (steatosis) corticosteroids	Histopathology Lung biopsy	Lung	ITZ	Alive
HC Perez del Nogal G [43]	USA	1	M/61	Diabetes mellitus, obesity, hypertension, hypothyroidism	Urinary antigen, serology	Lung	AMB	Alive
BM Nasim R [25]	USA	1	F/24	Post-partum. Lives in endemic area	Blastomycosis markers without specifications	Lung (parenchymal consolidation)	AMB—L	Alive
PCM De Macedo PM [28]	Brazil	1	M/19	Lives in endemic area	Histopathology-inguinal lymph node and serology	Pulmonary pleural and pericardial effusion, mediastinal and peritoneal lymph. Hepatosplenomegaly and skin	AMB	Alive

CM coccidioidomycosis, *HC* histoplasmosis, *BM* blastomycosis, *PCM* paracoccidioidomycosis, *USA* United States of America, *ARG* Argentina, *HIV* human immunodeficiency virus, *IDA* immunodiffusion assay, *CF* complement-fixation, *MNG* meningitis, *DM* diabetes mellitus, *CSF* cerebrospinal fluid, *FCZ* fluconazole, *IVZ* isavuconazole, *AMB -L* liposomal amphotericin B, *AMB – DC* amphotericin B deoxycholate, *AMB – LC* amphotericin B lipid complex, *ITZ* itraconazole

Paracoccidioidomycosis

Previously known as South American blastomycosis, paracoccidioidomycosis (PCM) is really a systemic fungal infection restricted to Latin America countries, from Mexico to Argentina. The highest prevalence is recorded in South America [26].

PCM has a significant impact on public health, affecting mainly the rural population. This is probably one reason why few co-infections with COVID-19 were reported. On the other hand, since SARS-COV-2 also affects the lungs, differential diagnosis with other illnesses with similar clinical manifestations is required. Unlike the reported situation for USA, where endemic diseases continued to be monitored during the pandemic era, this situation did not occur throughout all of Latin America. This was probably another cause of underdiagnoses. In Latin America, many countries with their health systems overcome, in many cases all attention was given to COVID-19 treatment. Even many reported deaths caused by COVID-19 were not informed considering its co-infection.

Although pre-existing pulmonary alterations caused by *Paracoccidioides* infection are an increased risk factor for severe cases of COVID-19, very few cases have been published. Some radiological overlaps that can be found in PCM and COVID-19 may delay the diagnosis of viral pneumonia co-infection but also to mask the underlying disease when the search for SARS-COV-2 was prioritized. Furthermore, several cases presumably diagnosed as COVID-19 were actually PCM, not only because of their lung lesions, but also because of their oral manifestations [27].

One case, as nosocomial infection in a patient with acute juvenile PCM, was reported in Brazil (see Table 2) [28]. If there were other cases in Latin America, we have not found any reports about them. SARS-CoV-2 coinfections with *Blastomyces* and *Paracoccidioides* were and remain less clear, with very few reported cases, but would not be unexpected in the appropriate clinical context [29].

Discussion

Fungal infections can cause signs and symptoms similar to other respiratory illnesses, including COVID-19. This means a challenge to achieve the diagnosis.

SARS-CoV-2 infection has been associated with immune dysregulation, including lymphopenia [44], which could reduce the host's ability to regulate *Coccidioides* infection. Despite this fact, as of February 2021, no study has reported the reactivation of CM in COVID-19 patients. Likewise, emerging evidence suggests that COVID-19 infection might accelerate reactivation of latent tuberculosis [45]. Due to the similarity in the immunological response against fungi and mycobacteria, this consequence could also occur in EM. In addition, dexamethasone, a drug widely used in patients with severe COVID-19, increases the risk of severe mycoses [46].

COVID-19 generates high levels of inflammation in certain guests causing a high release of inflammatory cytokines and consequently considerable tissue damage. A raised level of inflammatory cytokines especially interleukin-6 (IL-6) was associated with severe lung injury in co-infected patients [47]. This situation could be a risk factor for fungal infections of the respiratory system and would increase the possibility that a usually asymptomatic primary infection could become symptomatic; it could also increase the possibility of secondary reactivations of this latent mycosis. For this reason, it is extremely important know the endemic areas, "think in fungal disease," and perform different diagnostic techniques to allow the differential diagnosis in patients from these areas. Unfortunately, during the first months of the pandemic when all attention was focused on COVID-19, few differential diagnostic tests were performed, which surely led to diagnostic delay or underdiagnosis of these and other pathologies especially in these neglected diseases [29, 48].

Seventy-eight patients suffering from COVID-19 were registered associated with an endemic systemic mycosis. CM was the prevalent mycosis followed by histoplasmosis. In the reviewed cases, highly variable diagnostic methodologies were used, from biopsies, respiratory samples, and serology to specific antigens, but all were useful. It would even seem that COVID-19 did not generate an increase in mortality from these mycoses.

Conclusion

The COVID-19 pandemic is in continuous evolution, which masked endemic systemic mycoses and continues to do so. While healthcare systems try to control the crisis, they should not forget about these fungal infections, which in many cases are already historically considered neglected. The need for diagnostic methods for early diagnosis and management of these fungal diseases in the context of COVID-19 should be emphasized.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Li Q, Guan X, Wu P, Wang X, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199–207. https://doi.org/10.1056/NEJMoa2001316.
2. WHO. Coronavirus Disease (COVID-19) pandemic. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed on 9 November 2020).
3. Guan WJ, Ni ZY, Hu Y, Liang WH, et al. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708–20. https://doi.org/10.1056/NEJMoa2002032.
4. García LF. Immune response, inflammation, and the clinical spectrum of COVID-19. Front Immunol. 2020;16(11):1441. https://doi.org/10.3389/fimmu.2020.01441.
5. Messina F, Marin E, Valerga M, Depardo R, et al. Infecciones fúngicas en pacientes con COVID-19. Actualizaciones en Sida e infectologia. Buenos Aires 2021;29(105):6–16. https://doi.org/10.52226/revista.v29i105.49
6. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, et al. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. Lancet Microbe. 2022;5247:1–10.
7.• Ashraf N, Kubat RC, Poplin V, Adenis AA, et al. Re-drawing the maps for endemic mycoses. Mycopathologia. 2020; 185: 843–865. **This publication highlights the extension of the geographic areas in some ME.**
8.•• Thompson GR 3rd, Le T, Chindamporn A, Kauffman CA, et al. Global guideline for the diagnosis and management of the endemic mycoses: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology. Lancet Infect Dis. 2021;21(12):e364-e374. https://doi.org/10.1016/S1473-3099(21)00191-2. **A new guideline update about diagnostic methods and systemic treatments.**
9. Griffiths J, Colombo AL, Denning DW. The case for paracoccidioidomycosis to be accepted as a neglected tropical (Fungal) disease. PLoS Negl Trop Dis. 2019;13(5):1–10.
10. Linder KA, Kauffman CA. Current and new perspectives in the diagnosis of blastomycosis and histoplasmosis. J Fungi. 2021;7(1):1–10.
11.• Pruksaphon K, Intaramat A, Ratanabanangkoon K, Nosanchuk JD, et al.Diagnostic laboratory immunology for talaromycosis (penicilliosis): review from the bench-top techniques to the point-of-care testing. Diagn Microbiol Infect Dis. 2020; 96(3): 114959 https://doi.org/10.1016/j.diagmicrobio.2019.114959. **Immunological tests for the diagnosis of talaromycosis, including a proposed novel rapid point-of-care assay.**
12. Samaddar A, Sharma A. Emergomycosis, an emerging systemic mycosis in immunocompromised patients: current trends and future prospects. Front Med (Lausanne). 2021;23(8): 670731. https://doi.org/10.3389/fmed.2021.670731.
13. Teixeira MM, Barker BM. Use of population genetics to assess the ecology, evolution, and population structure of Coccidioides. Emerg Infect Dis. 2016;22(6):1022–30. https://doi.org/10.3201/eid2206.151565.
14. Heaney AK, Head JR, Broen K, Click K, et al. Coccidioidomycosis and COVID-19 co-infection, United States, 2020. Emerg Infect Dis. 2021;27(5):1266–73. https://doi.org/10.3201/eid2705.204661.
15.•• Huff D, Ampel NM, Blair JE. Coccidioidomycosis and COVID-19 infection. An analysis from a single medical center within the coccidioidal endemic area. Mycopathologia. 2022; 15:1–6. https://doi.org/10.1007/s11046-022-00629-6. **This article presents the study with the highest number of patients.**
16. McKinsey DS, Pappas PG. Histoplasmosis: time to redraw the map and up our game. Clin Infect Dis. 2020;70(6):1011–3. https://doi.org/10.1093/cid/ciz327.
17. Mittal J, Ponce MG, Gendlina I, Nosanchuk JD. Histoplasma capsulatum: mechanisms for pathogenesis. Curr Top Microbiol Immunol. 2019;422:157–91. https://doi.org/10.1007/82_2018_114.
18. Messina FA, Corti M, Negroni R, Arechavala A, et al. Histoplasmosis en pacientes con SIDA sin manifestaciones cutáneo-mucosas [Histoplasmosis in AIDS patients without tegumentary manifestations]. Rev Chilena Infectol. 2018;35(5):560–5. https://doi.org/10.4067/s0716-10182018000500560.
19. Tobón AM, Gómez BL. Pulmonary histoplasmosis. Mycopathologia. 2021;186(5):697–705. https://doi.org/10.1007/s11046-021-00588-4.
20. Qin Y, Huang X, Chen H, Liu X, et al. Burden of talaromyces marneffei infection in people living with Hiv/Aids in Asia during art Era: a systematic review and meta-analysis. Bmc Infect Dis. 2020;20(1):551.
21. Chan JF, Lau SK, Yuen KY, Woo PC. Talaromyces (Penicillium) marneffei infection in non-HIV-infected patients. Emerg Microbes Infect. 2016;5(3): e19. https://doi.org/10.1038/emi.2016.18.
22. Schwartz IS, Kauffman CA. Blastomycosis. Semin Respir Crit Care Med. 2020;41(1):31–41.
23. Benedict K, Williams S, Beekmann SE, Polgreen PM, et al. Testing practices for fungal respiratory infections and sars-cov-2 among infectious disease specialists, united states. J Fungi. 2021;7(8):2–6.
24. Baddley JW, Thompson GR, Chen SCA, White PL, et al. Coronavirus Disease 2019-associated invasive fungal infection. Open Forum Infect Dis. 2021;8(12):1–11.
25. Nasim R, Prasad A, Nasim H. Postpartum COVID-19 complicated by blastomycosis infection. Chest. 2021;160(4):A274.
26. Restrepo A, Gómez BL, Tobón A. Paracoccidioidomycosis: Latin America's own fungal disorder. Curr Fungal Infect Rep. 2012;6(4):303–11.
27. Baldo ME, Raffaele RM, Da Silva Santos PS, Ramalho RT, et al. Diagnostic challenge in an individual with Paracoccidioidomycosis during hospitalization in times of COVID-19. Int J Innov Educ Res. 2022;10(2):149–58.
28. de Macedo PM, Freitas DFS, Varon AG, Lamas C da C, et al. COVID-19 and acute juvenile paracoccidioidomycosis coinfection. PLoS Negl Trop Dis. 2020;14(8):1–7.
29. Nargesi S, Bongomin F, Hedayati MT. The impact of covid-19 pandemic on aidsrelated mycoses and fungal neglected tropical diseases: why should we worry? PLoS Negl Trop Dis. 2021;15(2):1–5.
30. Krauth DS, Jamros CM, Rivard SC, Olson NH, et al. Accelerated progression of disseminated coccidioidomycosis following SARS-CoV-2 infection: a case report. Mil Med. 2021;186(11–12):1254–6. https://doi.org/10.1093/milmed/usab132.

31. Nassif EF, Maloney N, Conley AP, Keung EZ. Disseminated coccidioidomycosis following COVID-19 mimicking metastatic thoracic relapse of well-differentiated liposarcoma: a case report. Front Med (Lausanne). 2021;13(8): 715939. https://doi.org/10.3389/fmed.2021.715939.
32. Chang CC, Senining R, Kim J, Goyal R. An acute pulmonary coccidioidomycosis coinfection in a patient presenting with multifocal pneumonia with COVID-19. J Investig Med High Impact Case Rep. 2020;8:2324709620972244. https://doi.org/10.1177/2324709620972244.
33. Shah AS, Heidari A, Civelli VF, Sharma R, et al. The coincidence of 2 epidemics, coccidioidomycosis and SARS-CoV-2: a case report. J Investig Med High Impact Case Rep. 2020;8:2324709620930540. https://doi.org/10.1177/2324709620930540.
34. Chen JC, Wong D, Rabi S, Worswick S, et al. All that coughs is not COVID-19: a delayed diagnosis of disseminated coccidioidomycosis following Severe Acute Respiratory Syndrome Coronavirus 2 infection. Open Forum Infect Dis. 2021;8(7):ofab246. https://doi.org/10.1093/ofid/ofab246.
35. Messina FA, Marin E, Caceres DH, Romero M, et al. Coronavirus Disease 2019 (COVID-19) in a patient with disseminated histoplasmosis and HIV-a case report from Argentina and literature review. J Fungi (Basel). 2020;6(4):275. https://doi.org/10.3390/jof6040275.
36. Basso RP, Poester VR, Benelli JL, Stevens DA, et al. COVID-19-associated histoplasmosis in an AIDS patient. Mycopathologia. 2021;186(1):109–12. https://doi.org/10.1007/s11046-020-00505-1.
37. de Macedo PM, Freitas AD, Bártholo TP, Bernardes-Engemann AR, et al. Acute pulmonary histoplasmosis following COVID-19: novel laboratorial methods aiding diagnosis. J Fungi (Basel). 2021;7(5):346. https://doi.org/10.3390/jof7050346.
38. Bertolini M, Mutti MF, Barletta JA, Falak A, et al. COVID-19 associated with AIDS-related disseminated histoplasmosis: a case report. Int J STD AIDS. 2020;31(12):1222–1224. https://doi.org/10.1177/0956462420957518.
39. Maldonado I, Elisiri ME, Fernández-Canigia L, Sánchez AV, et al. COVID-19 associated with disseminated histoplasmosis in a kidney transplant patient. Rev Argent Microbiol. 2021;S0325–7541(21):00121–8. https://doi.org/10.1016/j.ram.2021.10.006.
40. Stasiak CES, Nigri DH, Cardoso FR, Mattos RSAR, et al. Case report: incidental finding of COVID-19 infection after positron emission tomography/CT imaging in a patient with a diagnosis of histoplasmosis and recurring fever. Am J Trop Med Hyg. 2021;104(5):1651–4. https://doi.org/10.4269/ajtmh.20-0952.
41. Taylor M, Ghodasara A, Ismail A, Gauhar U, et al. Disseminated histoplasmosis in an immunocompetent patient after COVID-19 pneumonia. Cureus. 2021;13(8): e17269. https://doi.org/10.7759/cureus.17269.
42. Khanna A, Sinha AK, Kumar P, Pandey KK. Acute localized pulmonary histoplasmosis - another bug out of COVID's Pandora box! Lung India. 2022;39(1):91–2. https://doi.org/10.4103/lungindia.lungindia_590_21.
43. Perez Del Nogal G, Mata A, Ernest P, Salinas I. Disseminated histoplasmosis in an immunocompetent patient with COVID-19 pneumonia. BMJ Case Rep. 2022;15(1): e247617. https://doi.org/10.1136/bcr-2021-247617.
44. Liu J, Li H, Luo M, Liu J, et al. Lymphopenia predicted illness severity and recovery in patients with COVID-19: a single-center, retrospective study. PLoS ONE. 2020;15(11): e0241659. https://doi.org/10.1371/journal.pone.0241659.
45. Pathak L, Gayan S, Pal B, Talukdar J, et al. Coronavirus activates an altruistic stem cell-mediated defense mechanism that reactivates dormant tuberculosis: implications in Coronavirus Disease 2019 pandemic. Am J Pathol. 2021;191(7):1255–68. https://doi.org/10.1016/j.ajpath.2021.03.011.
46. Dellière S, Dudoignon E, Fodil S, Voicu S, et al. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. Clin Microbiol Infect. 2020;27(5):790.e1-5. https://doi.org/10.1016/j.cmi.2020.12.005.
47. Rubin EJ, Longo DL, Baden LR. Interleukin-6 receptor inhibition in Covid-19 - cooling the inflammatory soup. N Engl J Med. 2021;384(16):1564–5. https://doi.org/10.1056/NEJMe2103108.
48. Rodrigues ML, Nosanchuk JD. Fungal diseases as neglected pathogens: a wake-up call to public health officials. PLoS Negl Trop Dis. 2020;14(2):1–9.