June 15, 2022

INTRODUCTION

Welcome to the Second Annual Conference on Invasive Fungal Infections in Latin America. This webinar is organized by the MSGERC.

My name is Dr Marisa Miceli. I am a graduate of the University of Buenos Aires, Argentina, and I work in the Division of Infectious Diseases at the University of Michigan in Ann Arbor, Michigan, in the United States.

The aim of this webinar is to learn about your experiences with invasive mycoses.
We will explore your experiences, discuss them, find out what the difficulties are, and see how we can improve access to diagnosis and treatment for patients.

We thank the United States Centers for Disease Control and Prevention for supporting this initiative.

In this important open forum with colleagues from Latin America, we will discuss several topics, mainly histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and fungal diseases associated with COVID-19.

We will start with some questions to introduce the discussion and listen to your experiences. What are the local needs and obstacles? How we could we improve diagnosis and treatment?

HISTOPLASMOSIS

Question from Dr Miceli: *Have you noticed any difference in the "historical" endemic area for histoplasmosis? Are new areas of histoplasmosis seen? If so, why do you think this has occurred? In what population is histoplasmosis seen? Was histoplasmosis seen mainly in HIV-infected patients? Is this still the case now that there are more treatments for HIV? Or is it seen more in solid organ transplant patients or hematology-oncology patients? Or is it due to occupational exposure in immunocompetent patients or in patients with autoimmune diseases who are being treated with immunosuppressants? What is your experience in this matter?*

Response from Latin American participant: In a private clinic in Buenos Aires, we are not seeing cases of histoplasmosis in HIV, but our population is mostly renal transplant recipients.

Experience from Dr Miceli: In Michigan, which is an endemic area for histoplasmosis, many of our patients live in areas far from the city. They are exposed in rural areas, near lakes, or they do a lot of activity[activities] in forested areas.

- While immunocompromised patients are at increased risk, if the burden of exposure is very high, we also see immunocompetent patients developing histoplasmosis.
- We see virtually no HIV patients with histoplasmosis. In the last few years, I haven't seen any.
- What we see most is histoplasmosis in patients who have occupational exposure (gardeners, those who clean pools, those who trim leaves and branches)—those patients are the ones who present with pulmonary disease.
- In transplant recipients, we see more disseminated disease.

Question from Latin American participant*:* *How useful is the lateral flow urinary antigen test in the transplant population?*

Discussion (from Dr Miceli):

- Most of the lateral flow urinary antigen studies were performed in Latin America in HIV-infected patients, most of them with proven disseminated disease. In this population, the sensitivity and specificity were both very high, almost 96%.[1]
- The same test was studied in the United States, a multicenter work, including a great diversity of patients, with both probable and definite disease.
- The specificity was very high (about 95%), and the sensitivity was much lower (79%).[2]
- There were no patients with HIV in this study.
- It is likely that the difference in these performance results is because the fungal load of the patients studied in Latin America is very high:
    - HIV patients were severely immunosuppressed with disseminated disease and probably have a high burden of histoplasmosis. So, it is very likely that the sensitivity of the test is higher for that reason.
    - While the other study included solid organ transplant and immunocompetent patients with a mixture of probable and definite infection, very likely they had a lower fungal burden and that makes the sensitivity lower.
    - In the United States, the lateral flow is not used, given that the antigen test is available; it is performed in a reference laboratory, and the sensitivity and specificity are very high.
    - But if no other test available, and lateral flow is used, 79% of patients with histoplasmosis could be identified.

Question from Latin American participant: *What is the technique you use to test for histoplasmosis antigen?*

Response from Dr Miceli: The technique is the enzyme-linked immunoassay (EIA), and it is performed in serum and urine.

COCCIDIOIDOMYCOSIS:

Question from Dr Miceli: *I would like to know, in your experience, what is the spectrum of the disease? Does it occur more in the central nervous system or in other locations? Is there currently an increase in the number of cases? In what type of population does it occur? Is the HIV patient population still the main affected population? Or is there a shift in the affected population or demographics (eg, is it seen more in solid organ transplant or occupational exposure in immunocompetent patients)? In what geographic areas it is occurring?*

Response from Latin American participant:

- One patient with a skin lesion on the face has been reported in Córdoba (Argentina) (2018-2019). No new cases of coccidioidomycosis have been seen at the *Hospital de Clínicas* in Buenos Aires.
- Cordoba was not an endemic area, perhaps the patient lived or worked in another area of northwestern Argentina?

Experience from Dr Miceli:

- Michigan is not an endemic area, but we have patients due to internal migration, from endemic areas such as California and Arizona. They come in years later with reactivation in unusual locations, such as a patient with hip osteomyelitis due to coccidioidomycosis, diagnosed by biopsy.

PARACOCCIDIOIDOMYCOSIS

Question from Dr Miceli:

Paracoccidioidomycosis is an infection that people are not very aware of, it is usually not included in the differential diagnosis. I would like to know your experience with paracoccidioidomycosis. Is it on the radar of ID physicians or general practitioners? Or, are the cases you have seen chronic cases of many years, and the patient was never diagnosed? And if so, what can be done to change this situation?

Response from Latin American participants:

- In Buenos Aires, at *CEMIC,* paracoccidioidomycosis cases are not usually seen.
- It is still a disease that comes to Buenos Aires from endemic areas.
- In the *Hospital de Clínicas* in Buenos Aires, we have had in recent years 5% of patients coming from non-endemic areas.
- In general, the infection is almost 50% multifocal and is seen in patients arriving from the interior of the country.
- In the last year, we have seen co-infection of paracoccidioidomycosis with leishmaniasis.

Experience from Dr Miceli: I personally remember seeing only one case of paracoccidioidomycosis. This patient was from Corrientes (Argentina), and for years they

had been trying to diagnose him thinking it was anything else but paracoccidioidomycosis. Finally, in Corrientes, they did a biopsy, and paracoccidioidomycosis was diagnosed, but he already had the diagnosis when he arrived in Buenos Aires for treatment.

Question from Dr Miceli: *Do the patients come with or without a diagnosis of paracoccidioidomycosis? What about treatment? Are they given itraconazole and the patient returns to their place of origin? Can they continue with the treatment or is access to itraconazole a problem? What is the form of itraconazole, capsules or liquid solution?*

Response from Latin American participant:

- They come without diagnosis and are diagnosed in Buenos Aires.
- They usually go back to their place of origin, because it is cheaper, and continue treatment.
- Itraconazole is used as capsules.

Question from Dr Miceli: *Do they have access to SUBA itraconazole?*

Response from Latin American participant:

- There is no access to SUBA itraconazole due to its cost.

Experience from Dr Miceli: In fact, SUBA itraconazole is not used frequently in the United States because it is very expensive. Only if insurance covers it and, in cases where absorption is a problem, it can be given.

COVID-ASSOCIATED Invasive Fungal Infections (IFIs)

Question from Dr Miceli*: With regard to the diseases associated with COVID-19, now that COVID-19 is more manageable, there are more people vaccinated. At one point it emerged that fungal diseases were very common with COVID-19. It was not the experience we had in my hospital here in Michigan. But we know that COVID-19 associated pulmonary aspergillosis is a new entity. The experience in India was also noted, with so many mucormycosis and COVID-19 cases. Was that the case for you? Did you see a resurgence of fungal diseases in COVID-19 patients? Was it a problem for you or not?*

Response from Latin American participant:
In Argentina, we saw COVID-19 with invasive candidiasis, aspergillosis (during the first wave mainly), and only 1 mucormycosis case.

Question from Dr Miceli: *I would like to know if you have seen any fusariosis in patients with COVID-19. Or is the incidence of* Fusarium *similar now vs pre-COVID-19?*

Response from Latin American participant:

- In Argentina, fusariosis is seen only in hematologic or bone marrow transplant patients.

Experience from Dr Miceli:

- In Michigan, I have not seen any cases of *Fusarium* spp. infection associated with COVID-19. I have seen aspergillosis associated with COVID-19 and not necessarily concomitant with COVID-19. Many times, the COVID-19 had already resolved, and after 2 to 3 weeks, the patient developed aspergillosis.

- Mucormycosis related to COVID has not been seen here in the hospital in Michigan, but of course, there are many cases of candidiasis/candidemia, and I have seen some cases of pneumocystis pneumonia and cryptococcosis related to COVID-19.
- My experience was that we see more COVID-related candidemia in coronary care or intensive care unit patients. This may be because these patients have more catheters, and are hospitalized longer, so the risk factor is high for candidiasis beyond COVID.

FUNGAL INFECTIONS IN IMMMUNOCOMPROMISED HOSTS

Question from Dr Miceli*:* *What is your experience with non-immunocompromised patients who develop fungal infections? Are there any trends you are seeing? Are there more patients who, without any risk factors, develop sinus mucormycosis? Such as patients with diabetes or who are on some other immunosuppressive agent, patients who you don't understand why they have developed the infections?*

Response from Latin American participant:
- In Buenos Aires (Argentina), in non-HIV patients, but who have autoimmune diseases, an increase in cryptococcosis and histoplasmosis is seen.
- In patients with diabetes, you have seen more cryptococcosis.
- In dialysis patients, you do not see as much fungal disease.
- Although it is not very frequent, dialysis patients are more predisposed to cryptococcosis.

Experience from Dr Miceli: In Michigan, in the last year, 3 or 4 patients had mucormycosis with a severe sinus infection and even required massive reconstructive surgery. All studies were done, including genetic studies, and we could not find the reason why they had mucormycosis.

PROPHYLAXIS FOR COVID-19—ASSOCIATED PULMONARY ASPERGILLOSIS

Question from Latin American participant: *What is your opinion about primary prophylaxis for aspergillosis in critically ill patients with COVID-19? (Knowing that at the moment there are few studies that showed a tendency to decrease in prevalence.)*

- In fact, how do you decide who is going to have prophylaxis? I think more than anything else it is to be alert, to make an early diagnosis.
- There are a couple of studies that are being done to find out if doing some kind of screening, like the strategies used in bone marrow transplants with galactomannan, you can diagnose early.
- As far as I know, primary prophylaxis is not being done and it seems that it is a little difficult to determine which patients would benefit from such a strategy.
- The problem with these studies is that, by the time they are being conducted, the incidence of COVID-19 is going down and the population that develops COVID is not the same as the one that developed COVID-19 and ended up in intensive care at the beginning of the pandemic.

- So, it will be very difficult to establish parameters to see who can benefit from strategies like that.

DOCUMENTING RESISTANT ORGANISMS

Question from a Latin American participant: *We do surveillance, but in Argentina we do not have* Candida auris*. Why do you think this is happening? Why don't we have it in the country?*

Response from Dr Miceli:

- In Michigan, we do not have *Candida auris* either, but the question is: are we looking for *Candida auris*, are we swabbing everyone who comes to the hospital? The answer is no. And you can't know if there is or not if you're not looking for it. That happens with other pathogens, which we say we don't have. But are we really looking for them?
- Most likely we are not looking for them because they do not have a clinical implication or because we have not seen patients with that infection.
- We say we don't have voriconazole-resistant *Aspergillus* or azole-resistant *Aspergillus*, but we don't actually test for resistance in every *Aspergillus* that grows.
- Some we have tested and they have been negative. I do not know if we do not have resistant *Aspergillus* in the environment or if there are patients for whom we do not reach a microbiological diagnosis and that do not respond to azoles. We will never know that.
- Therefore, it is a matter of vigilance and when it becomes an identifiable clinical problem.

References

1. Cáceres DH, Gómez BL, Tobón ÁM, et al. Validation and concordance analysis of a new lateral flow assay for detection of *Histoplasma* antigen in urine. *J Fungi (Basel)*. 2021;7(10):799.
2. Abdallah W, Myint T, LaRue R, et al. Diagnosis of histoplasmosis using the MVista *Histoplasma* galactomannan antigen qualitative lateral flow-based immunoassay: a multicenter study. *Open Forum Infect Dis*. 2021;8(9):ofab454. Published 2021 Aug 31. doi:10.1093/ofid/ofab454