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ORIGINAL ARTICLE

Aspergillosis: Case Series from the Central Public Health Laboratory–Ministry of Health. Asunción, Paraguay. Period 2000–2019

Gustavo Aguilar[1], Patricia Araujo-López[1], Graciela Lird[2], Rocío Arguello[3], Raquel Blasco[4]

[1] Biochemist, Department of Bacteriology and Mycology, Public Health Central Laboratory, Asunción, Paraguay.
[2] Biochemist, Central Laboratory - Department of Microbiology, Hospital de Clínicas, San Lorenzo, Paraguay.
[3] Biochemist, Department of Microbiology, Hospital General Pediátrico Acosta Ñu, San Lorenzo, Paraguay.
[4] Biochemist, Bacteriology Service, Hospital Regional de Ciudad del Este, Paraguay.

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Correspondence:
Gustavo Aguilar;
gustavomicologiapy@gmail.com

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ABSTRACT

Introduction: Aspergillosis is an opportunistic mycosis with significant impact on immunocompromised patients; available data in Paraguay are scarce.

Objectives: To characterize patients diagnosed with aspergillosis whose samples were sent to the Mycology section of the Central Public Health Laboratory during the period 2000–2019.

Methods: A descriptive, retrospective study of clinical records from patients with positive specimens for *Aspergillus* genus.

Results: The study found 54 patients diagnosed with aspergillosis: 21 with otomycosis (38.9%), 17 with chronic pulmonary aspergillosis (31.5%), 5 with acute and chronic sinusitis (9.2%), 4 with invasive aspergillosis (7.4%), 3 with onychomycosis (5.6%), 2 with allergic bronchopulmonary aspergillosis (3.7%), and 2 with keratitis (3.7%). There were 56 isolates: 26 *Aspergillus* section *fumigati* (46.4%), 15 A. section *flavi* (26.8%), 13 A. section *nigri* (23.2%), 1 A. section *terrei* (1.8%), and 1 *A. glaucus* (1.8%). Microbiological diagnostic methods included fresh examination, staining, culture, and serology testing.

Conclusions: Multiple cases of aspergillosis were reported over a 20-year period. Otomycosis, predominantly in adults, was the most prevalent form of aspergillosis. In chronic rhinopulmonary forms, tuberculosis, tumors, chronic obstructive disease, cystic fibrosis, and asthma were the predisposing factors. Invasive aspergillosis was predominantly observed in pediatric patients, with autoimmune diseases and leukemias being the primary risk factors. Aspergillus section *fumigati* was the predominant isolate, followed by *Aspergillus* section *flavi* and *Aspergillus* section *nigri*.

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ARTÍCULO ORIGINAL

Aspergilosis: Casuística del Laboratorio Central de Salud Pública-Ministerio de Salud. Asunción, Paraguay. Período 2000-2019

Gustavo Aguilar[1], Patricia Araujo-López[1], Graciela Lird[2], Rocío Arguello[3], Raquel Blasco[4]

[1] Bioquímico/a, Departamento de Bacteriología y Micología, Laboratorio Central de Salud Pública, Asunción- Paraguay.
[2] Bioquímica, Laboratorio Central - Departamento de Microbiología, Hospital de Clínicas, San Lorenzo-Paraguay.
[3] Bioquímica, Departamento de Microbiología, Hospital General Pediátrico Acosta Ñu, San Lorenzo-Paraguay.
[4] Bioquímica, Servicio de Bacteriología, Hospital Regional de Ciudad del Este-Paraguay.

INFORMACIÓN ARTÍCULO

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Correspondencia:
Gustavo Aguilar;
gustavomicologiapy@gmail.com

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RESUMEN

Introducción: la aspergilosis es una micosis oportunista con gran impacto en pacientes inmunodeprimidos; los datos disponibles en Paraguay son escasos.

Objetivos: caracterizar a los pacientes con diagnóstico de aspergilosis cuyas muestras fueron enviadas a la sección de Micología del Laboratorio Central de Salud Pública en el período 2000-2019.

Materiales y métodos: estudio descriptivo y retrospectivo de fichas de pacientes con muestras positivas del género *Aspergillus*.

Resultados: se encontraron 54 pacientes con diagnóstico de aspergilosis: 21 con otomicosis (38,9 %), 17 con aspergilosis pulmonar crónica (31,5 %), 5 con sinusitis aguda y crónica (9,2 %), 4 con aspergilosis invasiva (7,4 %), 3 onicomicosis (5,6 %), 2 con aspergilosis broncopulmonar alérgica (3,7 %) y 2 con queratitis (3,7 %). Los aislamientos fueron 56: 26 Aspergillus sección *fumigati* (46,4 %), 15 A. sección *flavi* (26,8 %), 13 A. sección *nigri* (23,2 %), 1 A. sección *terrei* (1,8 %) y 1 A. *glaucus* (1,8 %). Los métodos de diagnóstico microbiológico fueron el examen en fresco, coloraciones, cultivo y serología.

Conclusiones: en un período de 20 años varios casos de aspergilosis fueron informados. La otomicosis con predominio en adultos fue la forma de aspergilosis prevalente. En las formas crónicas rinopulmonares, la tuberculosis, los tumores, la enfermedad obstructiva crónica, las fibrosis quísticas y el asma fueron los factores predisponentes. La aspergilosis invasiva fue predominante en pediatría, donde las enfermedades autoinmunes y las leucemias fueron los principales factores de riesgo. *Aspergillus* sección *fumigati* fue prevalente del total de aislamientos, seguido de *Aspergillus* sección *flavi* y *Aspergillus* sección *nigri*.

INTRODUCTION

The genus *Aspergillus* consists of saprophytic filamentous fungi that develop in any type of organic matter. In humans, they produce opportunistic infections, with species of the *fumigati, flavi* and *nigri* sections being isolated in more than 90% of the cases. Conidia enter by inhalation into the lungs reaching the alveoli, where they remain as saprophytes, but sometimes they act as allergens producing a form of allergic bronchopulmonary aspergillosis (ABPA) or allergic alveolitis. Another common form is chronic pulmonary aspergillosis (CPA), which affects approximately three million people; without treatment, this infection has a high probability of causing death within five years (1,2).

Angioinvasion and invasive aspergillosis (IA) occur when phagocytic defenses decrease due to various causes of immunosuppression in the patient: transplants, chemotherapies, high doses of corticosteroids and cancer patients. Although probably underestimated, global data show an annual incidence of 300,000 cases of IA, with a mortality between 30% and 80%, and a population at risk of 10 million people worldwide (1). In Latin America, Brazil (3), Chile (4,5), Colombia (6,7), Mexico (8), Uruguay (9), and Venezuela (10) reported cases of invasive fungal diseases in periods of several years, including cases of invasive aspergillosis. This is very similar to data reported in the USA and Europe (11–13) as regards clinical findings, predisposing factors and fungal agents identified. The difference was that, in the latter, due to their economic situation, newer antifungals were available and mycological diagnosis was carried out with molecular methods in most cases.

The treatment of invasive mycoses such as IA generates significant costs to the healthcare system. In a study in Chile in a high complexity pediatric hospital between 2015 and 2016, Barraza M. *et al.* (14) found that the costs in prescribed antifungal drugs, mainly voriconazole and liposomal amphotericin B, for invasive mycoses with the category of probable corresponded to 12% of the total pharmacy budget of that hospital. Hospitalization expenses, medical fees, and the costs of laboratory and imaging studies would still have to be added to that.

In Paraguay, reported data on the incidence of aspergillosis are scarce. The objective of this study was to characterize patients with aspergillosis with positive results for the *Aspergillus* genus in samples sent by healthcare institutions to the Mycology section of the Central Public Health Laboratory in Asunción, Paraguay.

MATERIALS AND METHODS

An observational, descriptive and retrospective study was conducted by reviewing patient records with clinical samples related to aspergillosis sent to the Mycology section of the Central Laboratory of Public Health in Asunción, Paraguay, in the period 2000–2019. The sex, age, symptoms, signs, and underlying diseases of patients, and the results of mycological studies (fresh examination, staining and culture) were recorded.

To include respiratory samples in the study, we considered the type of patient and selected those for whom both fresh examination and serial cultures were positive for the fungus. On the other hand, for the study of nail aspergillosis, we selected patients with an evolution of more than 1 year, with hyaline septate hyphae observed in fresh examination and a high count in culture, without isolation of dermatophyte fungi or of the genus *Candida* or related species.

Macroscopic and microscopic identification of isolates was performed using different photographic atlases and algorithms from reference texts (15,16). Direct examination of the samples was carried out using 40% potassium hydroxide (KOH), in addition to Giemsa and Gram stains. The primary and specific isolation media used for macro- and microscopic studies were 1/10 Sabouraud dextrose agar with chloramphenicol, potato dextrose agar, oatmeal and Czapek agar.

As for serology, identification of *Aspergillus fumigati, flavi* and *nigri* sections was performed by the double immunodiffusion method, using antigens provided by the Malbrán Institute of Argentina. The results of the nominal variables were expressed as percentages, while the numerical variables were presented as mean ± standard deviation. For data analysis, the software used was Excel 2019 from Microsoft Office.

RESULTS

A total of 54 cases of patients with aspergillosis from the period 2000–2019 were studied. Data on the forms of aspergillosis and their clinical presentation, risk factors, medical diagnosis, type of specimen analyzed, microscopic and culture examinations are presented in Table 1.

Table 1. Data of patients with samples sent to the Central Public Health Laboratory that resulted positive for *Aspergillus*. Asunción, Paraguay: period 2000–2019

Form of aspergillosis (n = number of cases)	Age (years)	Clinical presentations* (%)	Predisposing condition* (%)	Clinical samples (%)	Isolate n(%)
Otomycosis (n=21)	45.1 ± 15.9	Serous secretion (61.9) Itching (52.3) Mild pain (14.2)	Chronic otitis (9.5) Chronic use of corticosteroids (9.5)	Ear secretions	*Aspergillus* section *nigri* 13 (59.1) *A.* section *flavi* 8 (36.4) *Aspergillus glaucus* 1 (4.5)
Chronic pulmonary aspergillosis (n=17)	51.8 ± 22.4	Cough (64.7) Chronic expectoration (64.7) Hemoptysis (41.1) Sibilant rales (29.4)	Tuberculosis (29.4) Tumor (17.6) COPD (11.7) Cystic fibrosis (11.7)	Serum (41.1) Sputum (35.4) Lung biopsy (23.5)	*A.* section *fumigati* 15 (80) *A.* section *flavi* 3 (20)
Invasive aspergillosis (n=4)	10.3 ± 8.7	Prolonged fever (50) Dyspnea (25) Hemoptysis (25) Neurological symptoms (25)	Autoimmune disease (75) Acute leukemia (25)	Skin lesions (50) BAL (25) Biopsy (25) Serum (25)	*A.* section *fumigati* 4 (100)
Chronic sinusitis (n=4)	64 ± 12.6	Chronic nasal secretion (100) Headache (50) Laryngitis (25) Chronic tracheitis (25)	Type 1 diabetes (25)	Paranasal sinuses puncture	*A.* section *fumigati* 3 (75) *A.* section *flavi* 1 (25)
Onychomycosis (n=3)	55.6 ± 15.3	Hyperkeratosis and dark nail coloration	HIV+ (33)	Nail scraping	*A.* section *flavi* 2 (66.7) *A.* section *terrei* 1 (33.3)
Allergic bronchopulmonary aspergillosis (n=2)	20.5 ± 17.6	Dry cough (100) Difficulty breathing (100) Chronic expectoration (100)	Cystic fibrosis (50) Asthma (50)	Sputum	*A.* section *fumigati* 2 (100)

Table 1. Data of patients with samples sent to the Central Public Health Laboratory that resulted positive for *Aspergillus*. Asunción, Paraguay: period 2000–2019 (Continuation)

Form of aspergillosis (n = number of cases)	Age (years)	Clinical presentations* (%)	Predisposing condition* (%)	Clinical samples (%)	Isolate n(%)
Keratitis (n=2)	56.5 ± 7.7	Ocular pain (100) Vision loss (100)	Ocular trauma	Corneal scraping	*A*. section *fumigati* 1 (50) *A*. section *flavi* 1 (50)
Acute sinusitis (n=1)	28	Nasal polyps Abundant nasal secretions	Nasal septum deviation	Maxillary sinus puncture	*A*. section *fumigati* 1 (100)
Colonization (n=18)	52.6 ± 19.2	No symptoms related to aspergillosis	ICU admission with antibiotics (50) HIV+ (18.7) Chronic use of corticosteroids (12.5)	Sputum (43.8) Tracheal secretion (37.5) BAL (18.7)	*A*. section *fumigati* 13 (72.2) *A*. section *flavi* 5 (27.8)

* According to the available patient data
Source: own elaboration

As regards patients with otomycosis, which was the most prevalent clinical form of aspergillosis in our cases, one of them presented both *Aspergillus glaucus* and *A.* section *flavi*. In the vast majority of cases the predisposing causes were not known. Two patients had a history of chronic otitis and other two of chronic use of corticosteroids.

In chronic pulmonary aspergillosis (CPA), the *fumigati* section was prevalent. In one of the two pediatric patients with cystic fibrosis two different sections were isolated: *fumigati* and *flavi*. Among the predisposing causes of CPA related to tumors, we found lung and pancreas cancer, as well as type 1 diabetes, prolonged use of corticosteroids and aspergilloma, each in a different patient. In three patients of the CPA cases we observed prolonged fever and weight loss. In the four patients with IA (one 22-year-old, two 9-year-olds and one 1-year-old) we observed weight loss and skin ulcers. One person had acute leukemia and three had autoimmune diseases: two with chronic granulomatous disease and one with systemic lupus erythematosus. All patients had been receiving treatment with corticosteroids for years.

Acute sinusitis presented in one person, while four patients presented with the chronic form of the illness. The *fumigati* section was prevalent in cultures. As regards onychomycosis, one case involved hand nails and two involved toenails (*hallux*), with one of them being an HIV carrier. In the two patients with ABPA, aged 8 and 33 years, abundant Charcot-Leyden crystals with more than 25 leukocytes per field were observed in a fresh examination of sputum. The adult patient had an IgE titer > 3000 U. In addition, we found eighteen patients with a positive specimen in fresh examination and culture for the genus *Aspergillus*, but since their clinical manifestations and conditions were unrelated to clinical aspergillosis, we considered these cases as colonization (Table 1).

DISCUSSION

Otomycosis is an infection of the epithelium of the external auditory canal caused by filamentous fungi, mainly *Aspergillus*, and yeasts such as *Candida*. These fungi are colonizing in general, but

humid conditions, long-term use of antibiotics and corticosteroids, lack of hygiene, and exposure to dust and foreign bodies favor their abnormal growth, thus causing infection (17). In our study, all cases were adults, as has also been reported in other studies (18,19). Ear serous secretion and itching were the most common symptoms in both our patients and those of other studies (18–20). One of the predisposing factors identified was chronic use of corticosteroids, which could affect immunity, as mentioned also by Satish *et al.* (19). Otomycosis was the most frequent form of aspergillosis we found in the patients of this study, and more than half of the strains we identified were *Aspergillus* section *nigri,* followed by *A. flavi*, which is consistent with the findings of other authors in America and Asia (18–20). Treatment recommendations include controlling predisposing factors, local debridement and use of antifungal drugs such as clotrimazole (21).

In chronic pulmonary aspergillosis (CPA) the approximate age range of our patients was 30 to 70 years. This range is similar to those reported by other authors (22,23). Chronic pulmonary aspergillosis is normally associated with patients with tuberculosis and chronic obstructive pulmonary disease (COPD). According to Denning *et al.,* tuberculosis is associated with 20% of CPA cases (24). Similarly, in Africa, 61.3% of patients with tuberculosis were reported to have CPA (22). In our study, we observed that 29.4% of patients with CPA had tuberculosis. In Paraguay, according to data from the Ministry of Health, 2,115 new cases of pulmonary tuberculosis were recorded in 2019, for a total of 15,000 patients up to that year. The incidence in the country in 2019 was of 30 cases per 100,000 inhabitants, while in the western region of the country it was of 80.4 cases per 100,000 inhabitants (25).

COPD patients constitute a great percentage of the population in many countries, since the disease is closely associated with tobacco use; that is why this disease contributes quite a lot to CPA cases. In this study, we report 11.7% of COPD cases in CPA patients. According to Macedo *et al.,* it is estimated that 15% of the total population with COPD develop CPA. In turn, of those patients hospitalized for CPA, 1.3% developed IA (23,26). In Paraguay, more than 10,000 people are diagnosed with COPD each year, with an average of 5,300 annual deaths (27).

Cough and chronic expectoration, together with hemoptysis, were the most common manifestations in our patients. These symptoms have also been reported by several authors for this form of aspergillosis (23,24). The main test for CPA diagnosis is the detection of precipitins or IgG anti-*Aspergillus* antibodies by the double immunodiffusion test (28,29). This serology is also used for monitoring the success or failure of treatment (28). Positive serology allowed us to define this form of aspergillosis in 41.1% of our cases. Also, the presence of septate hyaline hyphae at 45-degree angles and positive sputum culture (35.4%) were defining criteria in the diagnosis of our CPA cases.

Aspergillus section *fumigati* is the most frequent fungal isolate in CPA cases; this has been reported in Latin America, Europe and the USA, where it represents more than 90% of all cases (23, 26,30,31). In Africa and Asia, on the other hand, the most frequent isolates are *A.* section *flavus* and *A.* section *nigri* (32–34). In this study, 80% of the isolated strains were *A.* section *fumigati*, followed by *A.* section *flavi*. Treatment management for CPA must be multidisciplinary. In the vast majority of cases surgery is recommended, but this should be carefully evaluated on an individual basis considering lesion number and size, and the patient's underlying disease (28). For pre- and postoperative care, use of azoles is recommended to avoid possible invasion into adjacent tissues; itraconazole can be used as first-line therapy because of its low cost and good safety profile (28). If surgery is not possible, long-term treatment with azoles may prevent progression of lesions (e.g., fibrosis) and complications such as hemoptysis (28,35). Voriconazole (or posaconazole) can be administered in more serious situations (28,36). When treatment with azoles fails and surgery is not possible, direct instillation of amphotericin B or an azole (itraconazole, miconazole) in the

aspergilloma cavity is recommended (28). Hemoptysis is the most serious complication and can require arterial embolization (28).

As regards invasive aspergillosis (IA), most of our patients were pediatric. In comparison, a pediatric hospital in Uruguay reported 4 cases of IA, with a mean age of 8 years (9). In Colombia, several cases of invasive aspergillosis have been reported in pediatrics (37–40). In two other studies, pediatric patients represented 4.5% and 13.6% of total reported cases, respectively (7,13). IA is often implicated in transplant patients, those with various types of cancer receiving immunosuppressive therapy, persons with leukemia, and patients with immunity disorders undergoing treatment (11,41). In this study, the underlying systemic conditions were immunity disorders, followed by acute leukemia. Previous articles have reported that IA has been identified primarily in organ biopsy specimens, bronchoalveolar lavage (BAL), and sterile fluids (7,13).

In this study, examination of skin lesions by scarifications, and biopsies and cultures positive for the fungus facilitated mycological diagnosis, along with host factors and clinical manifestations, similar to other studies (7,13). Cutaneous manifestations of aspergillosis have been reported in some studies in Latin America and other parts of the world (4,7,42). In invasive aspergillosis, it has been reported that in Colombia and other Latin American countries, *A.* section *fumigati* was the most frequent isolate, followed by *A.* section *flavi, A.* section *nigri* and others (4,6–8). However, Wang *et al.* (43) in China reported that the incidence of invasive lung aspergillosis caused by *A.* section *flavi* was greater than that of *A.* section *fumigati* in patients with hepatitis B. *A.* section *flavi* has been isolated in a nosocomial outbreak from skin, mucusae and subcutaneous tissue (44). In our study, all the isolates were *A.* section *fumigati*.

According to the Infectious Diseases Society of America (IDSA) guidelines, the treatment of choice for invasive aspergillosis is voriconazole, and in pediatric patients the dose is higher. The blood concentration of this antifungal is variable for each patient, and therefore monitoring is important to ensure treatment success. Other alternatives are liposomal amphotericin B (recommended for empirical treatment), isavuconazole and posaconazole. Combination therapy can be used in patients with significant immunosuppression and in those with extensive infection (45).

Aspergillosis of the paranasal sinuses in its invasive form (of pulmonary origin) can manifest as the rhinocerebral form of mucormycosis. A fungus ball can also develop in the paranasal sinuses (11). The invasive form is observed in immunocompromised patients with risk factors similar to those of IA. The approximate age range of patients in our study was between 50 and 75 years, similar to previous studies (4,7). Likewise, in our study, the prevailing symptoms were chronic nasal secretion and headache, and only one patient had a known predisposing condition (type 1 diabetes mellitus). All mycological diagnoses (smear and culture) were performed by sinus puncture.

In Latin America, reports of paranasal sinus aspergillosis corresponded to 15% and 19% of total aspergillosis in two studies in Chile, respectively (4,5), and 3% in one study in Colombia (7); in these studies, the highest number of isolates was *A.* section *fumigati* followed by *A.* section *flavi*. In our study of 4 cases the ratio of isolates was similar. Treatments are generally debridement, antifungals such as voriconazole or isovuconazole, and reduction of immunosuppression (11). It is of great importance to differentiate mucormycosis from this form of aspergillosis, as voriconazole has no activity on fungi of the order Mucorales.

Azole resistance in *Aspergillus* has been reported in different countries around the world, further complicating treatment (46). This led the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) to publish a guideline for treatment that, according to the epidemiology of the region, recommends that the first line of treatment be liposomal amphotericin B or an azole plus echinocandin if resistance exceeds 10% (46).

Although more epidemiological studies are needed, in a study in several countries including Paraguay, Resendiz-Sharpe *et al.* reported an 8.3% (n = 3/36) of resistance to voriconazole of the environmental isolates of *Aspergillus* section *fumigati* in the country's capital city, Asunción (47). Voriconazole is the first-line antifungal for aspergillosis, and species in section *fumigati* are the most frequent isolates. This problem, coupled with the existing risk factors for aspergillosis in the country, is a matter of concern.

Reports of aspergillosis in Paraguay are scarce, and this is a reality shared by most Latin American countries. This may be due to several reasons, since this infection and other opportunistic mycoses are not notifiable; in addition, there is low clinical suspicion and knowledge of the infection, which leads to delays in diagnosis and in the initiation of timely treatment in vulnerable populations. It is necessary to raise awareness of this infection at various levels of the health sector.

CONCLUSION

A total of 54 patients with aspergillosis have been reported in our laboratory over a 20-year period. Otomycosis, predominantly in adults, was the most prevalent form of aspergillosis. In chronic rhinopulmonary forms, tuberculosis, tumors, chronic obstructive disease, cystic fibrosis, and asthma were the predisposing factors. Invasive aspergillosis was predominantly observed in pediatric patients, with autoimmune diseases and leukemias being the primary risk factors. *Aspergillus* section *fumigati* was the predominant isolate, followed by *A.* section *flavi* and *A.* section *nigri*. We reported the highest number of cases of aspergillosis in Paraguay, and, therefore, it is extremely necessary to provide all the information about this opportunistic infection to the governmental and health care sectors, and to the general population as well, for better decision-making.

ETHICAL ASPECTS

Patient-identifiable data were neither used nor disclosed in this study and were kept anonymous throughout the data analysis process. This project was approved by the Research Ethics Committee of the Central Laboratory of Public Health (CEI–LCSP, for its acronym in Spanish), administrative decision 207/2022 issued on July 15, 2022.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Segal BH. Aspergillosis. N Engl J Med [Internet]. 2009;360(18):1870-1884. https://doi.org/10.1056/NEJMra0808853
2. Bongomin F, Gago S, Oladele R, Denning D. Global and Multi-National Prevalence of Fungal Diseases – Estimate Precision. J fungi (Basel) [Internet]. 2017;3(4):57. https://doi.org/10.3390/jof3040057
3. Ferreira-Gomes FJ, Motta RR. Incidences of Aspergillus sp. infections in Brazil. Contrib cienc soc [Internet] 2023;16(12):29142–54. https://doi.org/10.55905/revconv.16n.12-004
4. Valenzuela P, Legarraga P, Rabagliati R. Epidemiología de la enfermedad fúngica invasora por hongos filamentosos en el período 2005 a 2015, en un hospital universitario en Santiago, Chile Rev chil infectol [Internet]. 2019;36(6):732-41. https://doi.org/10.4067/S0716-10182019000600732
5. Rabagliati R, Fuentes G, Guzmán AM, Orellana E, Oporto J, Aedo I, et al. Enfermedad fúngica invasora en pacientes hemato-oncológicos y receptores de trasplante de precursores hematopoyéticos bajo

la perspectiva de los criterios diagnósticos EORTC/MSG. Rev chil infectol [Internet]. 2009;26(3):212-9. https://doi.org/10.4067/S0716-10182009000400002

6. Valencia Y, Cáceres DH, de-Bedout C, Cano LE, Restrepo Á. Frequency of Invasive Fungal Disease in Adults: Experience of a Specialized Laboratory in Medellín, Colombia (2009-2015). J Fungi (Basel) [Internet]. 2020;6(1):39. https://doi.org/10.3390/jof6010039
7. Goyeneche A, Rodríguez-Oyuela J, Sánchez G, Firacative C. Clinical and Epidemiological Profile of Patients with Invasive Aspergillosis from a Fourth Level Hospital in Bogota, Colombia: A Retrospective Study. J Fungi (Basel) [Internet]. 2021;7(12):1092. https://doi.org/10.3390/jof7121092
8. Román-Montes CM, Gonzalez-Lara MF, Ponce de Leon A, Valenzuela-Almada MO, Rangel-Cordero A. 1696. Epidemiology, Clinical Characteristics and Outcomes of Invasive Aspergillosis in a Tertiary Care Hospital in Mexico. Open Forum Infect Dis [Internet]. 2019;6(Supp 2):S621. https://doi.org/10.1093/ofid/ofz360.1560
9. Notejane M, Barrios P, Lombardo V, Nogueira V, Fernández N, Giachetto G. Infecciones fúngicas invasivas en niños hospitalizados en un centro de referencia de Uruguay. Arch Pediatr Urug [Internet]. 2023;94(1):e205. Disponible en: http://www.scielo.edu.uy/scielo.php?script=sci_arttext&pid=S1688-12492023000101205
10. Lemus-Espinoza D, Maniscalchi MT. Micosis sistémicas en pacientes del estado Anzoátegui, Venezuela, 2009-2018. RSVM [Internet]. 2021;41(1-2):27-32. Disponible en: http://saber.ucv.ve/ojs/index.php/rev_vm/article/view/23965
11. Cadena J, Thompson GR, Patterson TF. Aspergillosis: Epidemiology, Diagnosis, and Treatment. Infect Dis Clin North Am [Internet]. 2021;35(2):415-34. https://doi.org/10.1016/j.idc.2021.03.008
12. Kanaujia R, Singh S, Rudramurthy SM. Aspergillosis: an Update on Clinical Spectrum, Diagnostic Schemes, and Management. Curr Fungal Infect Rep [Internet]. 2023;17:144-155. https://doi.org/10.1007/s12281-023-00461-5
13. Sarigüzel FM, Koç AN, Sağiroğlu P, Atalay MA, Borlu A, Canöz Ö, et al. Molecular epidemiology and antifungal susceptibilities of Aspergillus species isolated from patients with invasive aspergillosis. Rev Assoc Med Bras (1992) [Internet]. 2023;69(1):44-50. https://doi.org/10.1590/1806-9282.20220441
14. Barraza M, Barnafi N, Ortiz G, Torres JP, Coria P, Catalán P, et al. Evaluation of the prescription, consumption and costs of antifungal drugs in a pediatric hospital in Chile Rev Chilena Infectol [Internet]. 2018;35(4):351-7. https://doi.org/10.4067/s0716-10182018000400351
15. De Hoog GS, Guarro J, Gené J, Figueras MJ. Atlas of clinical fungi. 2ª ed. Reus, España: Centraabureau voor Schimmelcultures; 2000. Available from: https://www.atlasclinicalfungi.org/
16. Koneman E, Roberts G. Micología práctica de laboratorio. 3ª ed. Buenos Aires: Panamericana; 1987.
17. Linstrom C, Lucente F. Diseases of the external ear. In: Bailey J, Johnson T, Newlands D, editors. Head & neck surgery-otolaryngology. Philadelphia, PA: Lippincott Williams & Wilkins; 2014. p. 1987-2002.
18. Ali K, Hamed M, Hassan H, Esmail A, Sheneef A. Identification of fungal pathogens in otomycosis and their drug sensitivity: our experience. Int Arch Otorhinolaryngol [Internet]. 2018;22(4):400-3. https://doi.org/10.1055/s-0038-1626702
19. Satish HS, Viswanatha B, Manjuladevi M. A clinical study of otomycosis. IORS J Dental Med Sci [Internet]. 2013;5(2):57–62. https://doi.org/10.9790/0853-0525762
20. Alarid-Coronel J, Celis-Aguilar E, Escobar-Aispuro L, Muñoz-Estrada V. Otomycosis in inmuno competent patients: clinical and mycological features. Our experience with 40 cases. Clin Otolaryngol [Internet]. 2018:43(1):373-7. https://doi.org/10.1111/coa.12966
21. Jimenez-García L, Celis-Aguilar E, Díaz-Pavón G, Muñoz-Estrada V, Castro-Urquizo Á, Hernández-Castillo N, et al. Efficacy of topical clotrimazole vs. topical tolnaftate in the treatment of otomycosis. A randomized controlled clinical trial. Braz J Otorhinolaryngol [Internet]. 2020;86(3):300-7. https://doi.org/10.1016/j.bjorl.2018.12.007
22. Olum R, Osaigbovo II, Baluku JB, Stemler J, Kwizera R, Bongomin F. Mapping of chronic pulmonary aspergillosis in Africa. J Fungi (Basel) [Internet]. 2021;7(10):790. https://doi.org/10.3390/jof7100790
23. Guinea J, Torres-Narbona M, Gijón P, Muñoz P, Pozo F, Peláez T, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: Incidence, risk factors, and outcome. Clin Microbiol Infect [Internet]. 2010;16(7):870–7. https://doi.org/10.1111/j.1469-0691.2009.03015.x
24. Denning D, Pleuvry A, Cole D. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. Bull World Health Organ [Internet]. 2011:89(12):864-72. https://doi.org/10.2471/BLT.11.089441

25. Ministerio de Salud Pública y Bienestar Social. Indicadores Básicos de Salud [Internet]. Asunción, Paraguay; 2019. Disponible en: http://portal.mspbs.gov.py/digies/wp-content/uploads/2020/01/Indicadores-Basicos-de-Salud-IBS-2019.pdf
26. Macedo-Viñas M, Denning D. Estimating the burden of serious fungal infections in Uruguay. J Fungi (Basel) [Internet]. 2018;4(1):37. https://doi.org/10.3390/jof4010037
27. Ministerio de Salud Pública y Bienestar Social. Cada año, más de 10 mil paraguayos son diagnosticados con EPOC [Internet]. Asunción: Gobierno del Paraguay; 2020. [Consultado 2024 jun 03]. Disponible en: https://www.mspbs.gov.py/portal/22151/cada-antildeo-mas-de-10-mil-paraguayos-son-diagnosticados-con-epoc.html
28. Denning D, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Respir J [Internet]. 2016;47:45–68. https://doi.org/10.1183/13993003.00583-2015
29. Uffredi ML, Mangiapan G, Cadranel J, Kac G. Significance of Aspergillus fumigatus isolation from respiratory specimens of nongranulocytopenic patients. Eur J Clin Microbiol Infect Dis [Internet]. 2003;22:457–62. https://doi.org/10.1007/s10096-003-0970-y
30. Barac A, Kosmidis C, Alastruey-Izquierdo A, Salzer HJF. Chronic pulmonary aspergillosis update: a year in review. Med Mycol [Internet]. 2019;57:S104–9. https://doi.org/10.1093/mmy/myy070
31. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. Thorax [Internet]. 2015;70(3):270–7. https://doi.org/10.1136/thoraxjnl-2014-206291
32. Oladele RO, Irurhe NK, Foden P, Akanmu AS, Gbaja-Biamila T, Nwosu A, et al. Chronic pulmonary aspergillosis as a cause of smear-negative TB and/or TB treatment failure in Nigerians. Int J Tuberc Lung Dis [Internet]. 2017;21(9):1056–61. https://doi.org/10.5588/ijtld.17.0060
33. Rozaliyani A, Rosianawati H, Handayani D, Agustin H, Zaini J, Syam R, et al. Chronic pulmonary aspergillosis in post tuberculosis patients in Indonesia and the role of LDBio Aspergillus ICT as part of the diagnosis scheme. J Fungi [Internet]. 2020;6(4):318. https://doi.org/10.3390/jof6040318
34. Namusobya M, Bongomin F, Mukisa J, Olwit WK, Batte C, Mukashyaka C, et al. Chronic pulmonary aspergillosis in patients with active pulmonary tuberculosis with persisting symptoms in Uganda. Mycoses [Internet]. 2022;65(6):625–34. https://doi.org/10.1111/myc.13444
35. Agarwal R, Vishwanath G, Aggarwal AN, Garg M, Gupta D, Chakrabarti A. Itraconazole in chronic cavitary pulmonary aspergillosis: a randomised controlled trial and systematic review of literature. Mycoses [Internet]. 2013;56(5):559–70. https://doi.org/10.1111/myc.12075
36. Saito T, Fujiuchi S, Tao Y, Sasaki Y, Ogawa K, Suzuki K, et al. Efficacy and safety of voriconazole in the treatment of chronic pulmonary aspergillosis: experience in Japan. Infection [Internet]. 2012;40:661–7. https://doi.org/10.1007/s15010-012-0322-x
37. Restrepo-Gualteros SM, Jaramillo-Barberi LE, Rodríguez-Martínez CE, Camacho-Moreno G, Niño G. Aspergilosis pulmonar invasiva: reporte de un caso. Biomed [Internet]. 2015;35(2):171–6. Disponible en: https://revistabiomedica.org/index.php/biomedica/article/view/2357/2719
38. Blazicevich L, Camacho LMC, Carrizosa J, Cornejo W. Hallazgos clínicos y radiológicos de dos casos de aspergilosis del sistema nervioso central en niños. Rev Neurol [Internet]. 2003;36(7):632–5. https://doi.org/10.33588/rn.3607.2002436
39. Botero V, García VH, Delgado A, Aristizabal AM, Gomez C, Caicedo LA, et al. Aspergilosis pulmonar invasora en pacientes pediátricos con trasplante hepático, a propósito de una sobreviviente. Rev Chil Pediatría [Internet]. 2018;89(2):241–5. https://doi.org/10.4067/S0370-41062018000200241
40. Vargas-Soler J, Morales-Camacho WJM, Flórez-Rodríguez CXF, Navarro-Mejía JA, Guerrero CF, Morales-Camacho MA. Aspergillus flavus endocarditis in an immunocompetent child. Case Rep. Med Mycol Case Rep [Internet]. 2018;22:48–51. https://doi.org/10.1016/j.mmcr.2018.08.003
41. Camargo JF, Husain S. Immune correlates of protection in human invasive aspergillosis. Clin Infect Dis [Internet]. 2014;59(4):569–77. https://doi.org/10.1093/cid/ciu337
42. Merad Y, Derrar H, Belmokhtar Z, Belkacemi M. Aspergillus genus and its various human superficial and cutaneous features. Pathogens [Internet]. 2021;10(6):643. https://doi.org/10.3390/pathogens10060643

43. Wang W, Zhao CY, Zhou JY, Wang YD, Shen C, Zhou DF, et al. Invasive pulmonary aspergillosis in patients with HBV-related liver failure. Eur J Clin Microbiol Infect Dis [Internet]. 2011;30:661–7. https://doi.org/10.1007/s10096-010-1137-2
44. Vonberg RP, Gastmeier P. Nosocomial aspergillosis in outbreak settings. J Hosp Infect [Internet]. 2006;63(3):246–54. https://doi.org/10.1016/J.JHIN.2006.02.014
45. Patterson TF, Thompson GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: Update by the Infectious Diseases Society of America. Clin Infect Dis [Internet]. 2016;63(4):e1–e60. https://doi.org/10.1093/cid/ciw326
46. Lestrade PPA, Meis JF, Melchers WJG, Verweij PE. Triazole resistance in Aspergillus fumigatus: recent insights and challenges for patient management. Clin Microbiol and Infect [Internet]. 2019;25(7):799–806. https://doi.org/10.1016/j.cmi.2018.11.027
47. Resendiz-Sharpe A, Dewaele K, Merckx R, Bustamante B, Vega-Gomez MC, Rolon M, et al. Triazole-resistance in environmental Aspergillus fumigatus in Latin America and African Countries. J Fungi (Basel) [Internet]. 2021;7(4):292. https://doi.org/10.3390/jof7040292