



Design of a Clinical Practice Guideline for the Prevention, Control, Diagnosis and Treatment of Fungemia in Adult Patients

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Abstract:

Introduction: Opportunistic fungal infections have become an important cause of morbidity and mortality in hospitalized patients. Most of the increase in these infections can be attributed to the increase in the use of new and more effective antibacterial agents, organ transplants, immunosuppressive and cytostatic therapies, the emergence of acquired immunodeficiency syndrome (AIDS) and the emergence of strains resistant to different antifungals. Most infections are attributable to *Candida*, *Trichosporon*, *Rhodotorula*, *Cryptococcus*, and *Geotrichum*. **Justification:** Through the construction of this guide, it is expected that the prevention, control, diagnosis and treatment of fungal infections in adult patients will have a positive impact on the control of risk factors, the more rational and cost-effective use of tools of the laboratory and antifungals. It lays the foundations for the creation of an active fungemia surveillance system in the country. **Scientific problem:** Increased morbidity and mortality of hospitalized adults as a result of invasive fungal infections. **Aim:** Design, develop, disseminate, implement and evaluate a Clinical Practice Guide applied to patients with suspected Fungemia to standardize prevention, control, diagnosis and appropriate treatment. The main result will be the design of a Clinical Practice Guide for the prevention, control, diagnosis and treatment of fungemia in adult patients which will offer recommendations based on the best evidence to reduce the variability in the diagnosis and treatment of this condition, reducing the complications of it.

Keywords: Fungemias, clinical practice guideline, opportunistic fungi, adult patients.

INTRODUCTION

Invasive fungal diseases (IFDs) are recognized as a global health concern by the World Health Organization and are caused by an increasing breadth of yeast, filamentous fungi, and dimorphic fungi pathogens. As fungi are ubiquitous in nature, clusters of infection can and have occurred, not only in the community but as nosocomial infection when there is transmission or acquisition of fungi in the healthcare environment (Fernández, 1998; Jawetz, 2014; Douglas, 2023; Bues et al, 2023).

There are over 300 million individuals affected by fungal infections worldwide. Recent multi-national analysis has estimated that fungal infections are killing 1.5 million cases annually. Invasive fungal infections (IFI) are rising due to many factors, including pathogenic strains, underlying medical conditions, early or late diagnosis, the choice of therapy, and drug resistance. With a delay in diagnosis and treatment or not achieving

effective therapeutic drug levels, IFI may develop into a chronic fungal infection (CFI). CFI tends to increase mortality if left untreated and increase resistance if not treated correctly (Khateb, 2023)

Patients admitted to Intensive Care Units (ICU) have a high risk of suffering from invasive mycoses. Among these, the prolonged stay in the ICU stands out, since the severity of the underlying disease is combined with the instrumentation, the progressive colonization of the patient (which increases dramatically after the eighth day), presence of a central venous catheter, acute kidney failure, use of broad-spectrum antibacterial or immunosuppressive drugs, diabetes, surgery (especially abdominal surgery), organ transplant, hemodialysis and acute pancreatitis. Furthermore, extreme ages (elderly and premature children), maintenance of colonized catheters, malnutrition and candidemia due to species other than *C. albicans* are indicators of poor prognosis. In mycoses caused by fungi other than *Candida*, neutropenia (*Aspergillus*), cellular immunodeficiency (*Cryptococcus* and *Pneumocystis*) and ketoacidosis or the use of chelators (zygomycetes) are proven predisposing factors. Fungemia, generally caused by *Candida spp.*, is the most common deep mycosis in critically ill patients and is often clinically indistinguishable from bacterial septicemia. Less frequently, respiratory or disseminated mycoses caused by *Aspergillus* or other filamentous fungi, such as *Scedosporium*, *Fusarium*, *Pneumocystis*, *Acremonium* or zygomycetes (*Mucor*, *Rhizopus*, *Rhizomucor* and *Absidia*), are also described in these patients, as well as meningeal or systemic manifestations caused by other yeast species (*Cryptococcus*, *Trichosporon*, *Saccharomyces* and *Rhodotorula*) (Vargas, 2023; Celis, 2023).

In recent years there has been an important epidemiological change in the etiology of invasive candidiasis and, although *Candida albicans* continues to be the predominant species in blood cultures, other species, such as *C. parapsilosis*, *C. glabrata*, *C. tropicalis* or *C. krusei*, represent between 35 and 55% of the isolates. The problem posed by this etiological drift is mainly therapeutic, since non-*albicans Candida* species may present less sensitivity and even resistance to the antifungals used in the treatment. In the ICU, invasive aspergillosis is more frequently observed in patients with chronic bronchopathy treated with glucocorticoids and its presence is considered an indicator of poor prognosis. Most aspergilloses are primarily pulmonary or cerebral and are usually caused (>80%) by *Aspergillus fumigatus*. Other species, such as *A. niger* and *A. flavus*, can also be isolated, but *A. terreus* is the species that poses the most therapeutic problems due to its lower sensitivity to antifungals. *Malassezia* species are known to cause superficial mycoses such as folliculitis. They are also known to cause invasive *Malassezia* infections such as bloodstream infections in neonates and immunocompromised patients, although rarely (Pemán, 2008, 2013; Díaz, 2015; Pfaller, 2016; Martínez, 2014; Maseda, 2016; Tashiro, 2023).

Invasive fungal infections (IFI) have become a problem for hospitals due to the increase in the spectrum of susceptible patients, the increase in the number of patients at risk and their high mortality. The microbiological diagnosis of IFI, mainly those caused by *Candida spp.*, is based on microbiological culture. Microbiology laboratories were undergoing dramatic changes in the last ten years and many techniques and specific culture media are now available. Another point of evolution is Multiplex PCR. Knowledge of the local epidemiology of the species causing candidemia is important when instituting empirical antifungal treatment due to the marked differences in antifungal sensitivity between species (Lengerova, 2023; Diaz, 2021; Ghoneim, 2024; Kim, 2020).

JUSTIFICATION

The number of patients with invasive fungal infections continues to increase, and the majority of infections are attributable to members of the fungal family, for example, *Candida*, *Trichosporon*, *Rhodotorula*, *Cryptococcus*, and *Geotrichum*. *Candida* species account for the majority of candidiasis in patients with predisposing factors. *Trichosporon* species are the second cause of fungemia in patients with hematological disorders. *Rhodotorula* species are associated with catheter infections, while *Cryptococcus* species infect AIDS patients. *Geotrichum* species are associated with immunocompromised patients. Depending on the species, mortality due to invasive fungal infections ranges between 15 and 80%. Added to this situation is the emergence of *Candida auris*, a multi-resistant pathogen, and it is worrying that *Candida* species are becoming less sensitive to fluconazole. Through the construction of the recommendations, it is expected that the prevention, control, diagnosis and treatment of fungal infections complications in adult patients will reaffirm the comprehensive approach to patients, and, at the same time, have a positive impact on the use more rational and cost-effective laboratory tools and antifungals. Likewise, it is an excellent opportunity to lay the foundations for the creation of an active fungemia surveillance system in the country. A systematic review of the medical literature was carried out to identify and summarize all publications related to fungemia in adults, as well as their clinical and epidemiological characteristics (Chowdhary, 2017; Arastehfar, 2018; De Pauw, 2008; Kothavade, 2010; Villar, 2022; Paudel, 2023; Sig, 2023)

The information search was carried out in the Pub-Med/Medline database of the National Library of Medicine (NLM/NCBI) and in the Scielo database. The search structures were designed using text words identified in relevant articles, keywords according to the database consulted, as well as Quick Reference Guides, practical manuals and care protocols. 266 research articles were reviewed from 1989 to 2019, 80% of them on candidiasis and 20% on other opportunistic fungi. Based on everything analyzed above, the scientific problem is defined as: Increase in morbidity and mortality of hospitalized adults as a consequence of invasive fungal infections. That's way we need to optimize the performance of Secondary Care health professionals in the event of fungemia in adults, which guarantees comprehensive, effective and quality medical care. The principal objective of this work is to design, develop, disseminate, implement and evaluate a Clinical Practice Guide applied to patients with suspected Fungemia to standardize prevention, control, diagnosis and appropriate treatment.

METHODOLOGY TO BE USED TO FACE THE PROBLEM

This is a technological development project in the Intensive Care Unit, Surgical, Clinical and Microbiology Services of the Holguín Military Hospital, in the Holguín Municipality, whose design is planned to be a quasi-experimental study based on the preparation of a Guide of Clinical Practice. The control of biases will be carried out by one of the researchers with the responsibility of evaluating the output information, which will allow double-blind masking of the information, the rest of the researchers and participants will not know these results. The use of two groups is planned, one for study or intervention to which the guide will be applied and the control group will be from a historical cohort. The universe will consist of all patients admitted to the Services of the Military Hospital of Holguín, with clinical symptoms of the disease and the sample will be those who respond to a series of established inclusion and exclusion criteria.

- The health interventions proposed by the guide will be given by:
 1. Admission of the patient to the aforementioned services.
 2. Clinical diagnosis of fungemia.
 3. Assessment of hemodynamic status and associated comorbidity.

4. Definition of associated risk factors.
 5. Indication of complementary and microbiological studies.
 6. Health intervention depending on the clinical pattern.
- These basic steps of the guide proposal will allow action on the patient depending on the clinical presentation.
 - A survey model will be carried out for the collection of primary data, an informed consent model will be prepared.
 - The creation of a consultation will be requested for the evaluation of these patients that will allow the clinical, epidemiological and microbiological aspects to be evaluated.
 - The following mycological studies will be carried out - Direct examination with 10% potassium hydroxide
 1. Cultivation and typing of filamentous fungi
 2. Cultivation and typing of dimorphic fungi
 3. Cultivation and typing of yeast fungi
 4. Use of the ATB FUNGUS 3

In a first stage, also corresponding to the first specific objective, the following will be carried out:

**Assessment of Its Design and Elaboration: For This, The Following Questions Will Be Raised:
*Bibliographic Review:***

- The bibliographic review must be extensive, including the most relevant articles in the main languages, and updated. This last aspect will be fundamental, because from the moment the preparation of a guide begins until the final recommendations are established, a period of time passes in which important articles that must be taken into account can be published.
- In some section of the CPG the bibliographic search strategy must be stated ("keywords" used, sources consulted and date range covered), to facilitate new implementations of the same.
- The fact that the authors can modify some of the recommendations will add quality to the CPG, leaving a record of this to be reviewed in a later update.
- Management options and their impact on patients:
- Whether the CPG is for prevention, control, diagnosis and treatment, it will be stated that all reasonable practical options and all potentially important clinical outcomes for the patient have been considered, including taking into account aspects of morbidity and mortality and influence on quality of life.

Propose To Our Patient a Series of Possibilities That Allow Us to Make Appropriate Decisions:

- It would be desirable to include a cost-effectiveness analysis of the recommendations; its presence represents added value to the CPG due to the difficulty in carrying it out and the economic implications that this may entail.

Structured Method to Establish Agreements on the Different Recommendations:

- It will be important that the elaboration group is made up of representatives of the different specialties involved in the topic, in order to contribute different points of view.
- Contributions from patients who, although not directly involved in its preparation, should at least be part of the final review of the CPG will be especially useful, since a recommendation may be of great interest to the clinician and not so much to them.

- The recommendations will arise after analyzing the levels of evidence of the scientific articles; however, their final writing will be the result of agreements between the members of the drafting group. Somewhere in the CPG it will be explicitly defined how these agreements were reached in order to assess possible biases in the choice of recommendations.

Expert Review and Verification:

- Once all the steps in preparing a guide have been completed, a review by external evaluators will be advisable, since if they consider it useful for their practice, its validity increases.
- When the evidence supporting the recommendations is weak, practical verification will be necessary. If its application improves the outcome in patients, we reinforce its usefulness.

Assess the Validity of the Recommendations. We Must Take into Account:

- The scale of evidence that will be used in the bibliographic review and how it will be related to the degrees of recommendation.
- Of course, the higher the quality of the bibliography, the higher the degree of recommendation. It is important to note that recommendations do not have to include all results related to the highest levels of evidence, but only those that are considered clinically relevant. In a second stage and in correspondence with its implementation and validation, it will be applied to the research or study group to subsequently establish comparisons with the historical cohort.

In summary, due to everything mentioned above, it is necessary to design a Clinical Practice Guideline for this disease, taking into consideration the following arguments:

- Variability of clinical practice, given by variation in the use of different health interventions in the same clinical situation.
- Variation in the consumption of available resources.
- Inequalities in the quality of care.
- Uncertainty in expected health outcomes
- Difficulties in assimilating and analyzing the large volume of existing information.

As output indicators we expect the following:

- Promptness in medical action by unifying action criteria and organizing the patient's critical path.
- Scientific evidence up to now verifiable in the literature will be applied.
- Reduction of in-hospital infections due to opportunistic fungi.
- Reduction in morbidity and mortality due to complications.
- Effective and specific treatment for each germ.

In the preparation of these guidelines, the aim is to review the secondary and tertiary prevention options that currently exist for the management of fungemia in hospitalized patients, based on an intelligent search strategy using Medline, Scielo, Clinical Evidence, PubMed, Google Scholar, ResearchGate, ScienceDirect, etc. For the classification of evidence, the proposal by the AHA / ACC of 2006 and other updated sources will be followed.

- Grade A: Evidence based on large randomized, controlled studies and systematic review, including meta-analysis.

- Grade B: High-quality, non-randomized studies, cases and controls or case series.
- Grade C: There is limited evidence. At least some acceptable study.
- Grade D: No evidence based on clinical studies. The recommendation is based solely on expert opinion.

SCIENTIFIC NEWS

Design of Clinical Practice Guides for the prevention, control, diagnosis and treatment of fungemia in adult patients based on a set of recommendations from systematic reviews of scientific evidence, with the aim of guiding health professionals and patients. in the decision-making process to select the most appropriate prevention, control, diagnostic and therapeutic interventions, in the context of secondary care.

THEORETICAL AND PRACTICAL CONTRIBUTIONS

The design of these guidelines is conditioned by the review of action protocols, quick reference guides and practical manuals on fungemia, taking as a starting point the difficulties in caring for patients with this condition in secondary care. From this, an idea was developed, the background of the problem was reviewed and the idea of its design was formed. It is then that we consider this objective problem when responding to a real need of society if we keep in mind that this disease progresses in incidence and as a cause of mortality, it is also specific, if we observe that it is focused on the comprehensive care of the patient and it is precisely in in this aspect, we justify the need for research. On the other hand, the aim is to reduce morbidity and mortality due to this risk factor, reduce them and guarantee effective and specific care (practical contribution). There is also the possibility of empirical testability of the topic., by accurately defining the terms necessary to understand the problem and contrasting it with other positions on the matter, keeping in mind the great heterogeneity of patients and the non-homogeneity in their diagnosis, treatment and follow-up, is that the need for a guide is essential (theoretical contribution).

PROJECT MANAGER'S EXPERIENCE RELATED TO THE MAIN OBJECTIVE OF THE PROJECT

Dr. Lilianne Dominguez Céspedes, First Degree Specialist in Microbiology, is the specialist of the mycology department, the topic constitutes her line of research, it was the subject of her residency completion thesis, she presents published works, presentations at provincial, national and international events. The members of the group of authors are specialists in the area under investigation.

MATERIAL RESOURCES AND INFRASTRUCTURE AVAILABLE BY THE ENTITIES TO EXECUTE THE PROJECT

The research will be carried out at the Holguín Military Hospital where there is a microbiology laboratory, rooms to develop workshops, connectivity to Intranet and Internet, as well as office materials at our disposal for daily work.

REFERENCES

Albuquerque OC, Hermosilla DG, Tapia PC. Distribución y susceptibilidad a fluconazol de levaduras del género *Candida* aisladas en pacientes hospitalizados y ambulatorios. *Rev chil infectol.* [Internet]. 2009 Oct [citado 2017 ene 19]; 26(5): 435-439. Disponible en: http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S071610182009000600007&lng=es.

Arastehfar A. et al. YEAST PANEL multiplex PCR for identification of clinically important yeast species: stepwise diagnostic strategy, useful for developing countries. *Diagnostic Microbiology and Infectious Disease* 93 (2019) 112 – 119. <https://doi.org/10.1016/j.diagmicrobio.2018.09.007>

- Bues, Florencia, Herrera, Fabián, Relloso, Silvia, Torres, Diego, Temporiti, Elena, Carena, Alberto, Forastiero, Agustina, & Bonvehí, Pablo. (2023). Etiology, clinical characteristics and outcomes of invasive fungal infection in patients with hematological malignancies in a university hospital in Argentina. *Revista chilena de infectología*, 40(6), 665-674. <https://dx.doi.org/10.4067/s0716-10182023000600665>
- Caldas, Z. J. Candida auris Características, Aspectos Farmacológicos y Epidemiológicos. <https://repository.unad.edu.co/handle/10596/57710>
- Canton E, et al. Métodos microbiológicos para el diagnóstico, manejo y estudio de la infección fúngica invasora. *Enferm Infecc Microbiol Clin*. 2013. <http://dx.doi.org/10.1016/j.eimc.2013.01.008>.
- Celis, F. (2023). Lista prioritaria de patógenos fúngicos de la Organización Mundial de la Salud para guiar la investigación, desarrollo y acciones de salud pública. *Boletín Micológico*, 38(1). <https://iieya.uv.cl/index.php/Bolmicol/article/download/3966/3816>
- Chowdhary A, Sharma C, Meis JF. Candida auris: a rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. *PLoS Pathog* 2017;13(5): 1–10. <https://doi.org/10.1371/journal.ppat.1006290>.
- Cuenca Estrella M. Antifúngicos en el tratamiento de las infecciones sistémicas: importancia del mecanismo de acción, espectro de actividad y resistencias. *Rev Esp Quimioter* [Internet]. 2010 [citado 2017 Mayo21]; 23(4):169-176. Disponible en https://www.researchgate.net/publication/277261113_Antifungicos_en_el_tratamiento_de_las_infecciones_sistemicas_importancia_del_mecanismo_de_accion_espectro_de_actividad_y_resistencias
- De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al.
- Díaz Martín A. Epidemiología y factores pronósticos de la candidemia en adultos. Identificación de factores para aislamiento de especies resistentes a azoles [Tesis Doctoral]. España: Universidad de Sevilla. Departamento de Medicina; 2015 nov [citado 2016 nov 21]. Disponible en: <https://idus.us.es/xmlui/handle/11441/41384>
- Díaz Martínez, J. V. (2021). Bacteriemia y fungemia en pacientes COVID-19: prevalencia de patógenos microbianos y sensibilidad antimicrobiana, en el Hospital III Daniel Alcides Carrión de ESSALUD–Tacna, junio 2020 a mayo del 2021. <https://repositorio.upt.edu.pe/handle/20.500.12969/2063>
- Douglas, A.P.; Stewart, A.G.; Halliday, C.L.; Chen, S.C.-A. Outbreaks of Fungal Infections in Hospitals: Epidemiology, Detection, and Management. *J. Fungi* 2023, 9,1059. <https://doi.org/10.3390/jof9111059>
- Espinel A. Mechanisms of resistance to antifungal agents: Yeasts and filamentous fungi. *Rev Iberoam Micol* [Internet]. 2008 Jun [citado 2017 Mayo21]; 25: 101-106. Disponible en: <https://www.ncbi.nlm.nih.gov/pubmed/18473504>
- Fernández Andreu CM, González Miranda M, Illnait Zaragozí MT, Martínez Machín G. Determinación de la concentración mínima inhibitoria de anfotericina B en levaduras de interés médico. *REV CUBANA MED TROP* 1998; 50(1):48-53.
- Ghoneim, E. M., Abd ElAziz, A. M., & Awad, S. M. (2024). Characterization of Nosocomial Fungal Infection among Hepatic ICU Patients in National Liver Institute. *Egyptian Journal of Medical Microbiology*, 33(1). https://journals.ekb.eg/article_326097.html
- Guirao Abad JP. Acción de la validamicina A y los antifúngicos de uso clínico, micafungina y anfotericina B, sobre *Candida albicans* [Tesis Doctoral]. España: Universidad de Murcia; 2016 [citado 2017 Mayo21]. Disponible en: <http://www.tesisenred.net/handle/10803/396102?locale-attribute=es>
- <https://journals.asm.org/doi/abs/10.1128/spectrum.03203-23>
- Jawetz E, Melnick JL, Adelberg EA. En: *Microbiología médica*. 26 ed. Estados Unidos: Interamericana editores; 2014. Cap 45. p. 1-79.

Khateb, A. M., Alofi, F. S., & Almutairi, A. Z. (2023). Increased prevalence of fungemia in Medina, Saudi Arabia. *Frontiers in Epidemiology*, 3, 1180331. <https://www.frontiersin.org/articles/10.3389/fepid.2023.1180331/full>

Kim, S. E., Jung, S. I., Park, K. H., Choi, Y. J., Won, E. J., & Shin, J. H. (2020). Case report: nosocomial fungemia caused by *Candida diddensiae*. *BMC Infectious Diseases*, 20(1), 1-4. <https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05095-3>

Kothavade RJ, Kura MM, Valand AG, Panthaki MH. *Candida tropicalis*: its prevalence, pathogenicity and increasing resistance to fluconazole. *J Med Microbiol* [Internet]. 2010 Aug [citado 2016 nov 17]; 59(Pt 8):873-80. Disponible en: <https://www.ncbi.nlm.nih.gov/pubmed/20413622>

Lengerova, G. B. (2023). *Evaluation of modern microbiological methods for rapid identification of microorganisms in patients with bacteremia and fungemia AUTHORS SUMMARY* (Doctoral dissertation, Medical University-Plovdiv). <https://mu-plovdiv.bg/wp-content/uploads/2022/12/Avtoreferat-ons-Lengerova-en.pdf>

Lobaina T. (2010) Métodos cromogénicos y fluorogénicos para el diagnóstico de especies de *Candida* de relevancia clínica. Tesis de Doctorado. Instituto de medicina tropical Pedro Kourí.

Martí Carrizosa M. *Candida parapsilosis*, *C. orthopsilosis* y *C. metapsilosis*: epidemiología de las candidemias, patrones de sensibilidad y mecanismos de resistencia a las equinocandinas [Tesis Doctoral]. Barcelona: Universidad Autónoma de Barcelona; 2015 [citado 2016 nov 17]. Disponible en: <http://ddd.uab.cat/record/132860>

Martínez S. Filamentación y actividad proteolítica como pruebas rápidas para la identificación del género *Candida* spp. de infecciones nosocomiales [Tesis Doctoral]. México: Universidad Autónoma de México: Toluca; 2014 [citado 2016 nov 21]. Disponible en: <http://ri.uaemex.mx/handle/20.500.11799/14985>

Maseda E. EPICO 3.0. Recommendations on invasive candidiasis in patients with complicated intra-abdominal infection and surgical patients with ICU extended stay. *Rev Iberoam Micol* [Internet]. 2016 Jul [citado 2017 Mayo21]; 33 (4): 196-205. Disponible en: <https://www.ncbi.nlm.nih.gov/labs/articles/27422492/>

Paudel, R. (2023). Emergence of *Candida auris* infection: A review. *Microbes and Infectious Diseases*. https://journals.ekb.eg/article_297680.html

Pemán García J. Aspectos epidemiológicos de las micosis en el paciente crítico. *Rev Esp Quimioter* 2008; 21(Núm. Ext. 1):7-8.

Pemán, J., & Salavert, M. (2013). Epidemiología y prevención de las infecciones nosocomiales causadas por especies de hongos filamentosos y levaduras. *Enfermedades Infecciosas y Microbiología Clínica*, 31(5), 328-341. <https://www.sciencedirect.com/science/article/pii/S0213005X13000256>

Pfaller MA, Castanheira M. Nosocomial Candidiasis: Antifungal Stewardship and the Importance of Rapid Diagnosis. *Med Mycol* [Internet]. 2016 Jan [citado 2016 nov 21]; 54(1): 1-22. Disponible en: <https://www.ncbi.nlm.nih.gov/pubmed/26385381>

Ramos Mendoza, L. F., & Espitia Acevedo, D. (2021). Infecciones micóticas asociadas a la atención en salud. <https://repositorio.unicordoba.edu.co/handle/ucordoba/4299>

Reyes I, Pérez L, Morffi M, Barletta J. Aislamiento de *Rhodotorula*. Presentación de un caso en paciente con leucemia mieloide aguda. *Medisur* [revista en Internet]. 2013 [citado 2017 Feb 10]; 11 (5): [aprox 3 p.]. Disponible en: <http://medisur.sld.cu/index.php/medisur/article/view/2542>.

Sig, A. K., Çetin-Duran, A., & Kula-Atik, T. (2023). Distribution of fungemia agents in five years and antifungal resistance. *European Review for Medical & Pharmacological Sciences*, 27(16). https://www.researchgate.net/profile/Ali-Korhan-Sig/publication/373515462_Distribution_of_fungemia_agents_in_five_years_and_antifungal_resistance/links/64efb6cc67890027e16f6b46/Distribution-of-fungemia-agents-in-five-years-and-antifungal-resistance.pdf

Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis.* 2008; 46:1813–21.

Tashiro, M., Takazono, T., & Izumikawa, K. (2023). Invasive *Malassezia* Infections. *Medical mycology journal*, 64(4), 79-83. https://www.jstage.jst.go.jp/article/mmj/64/4/64_79/_article/-char/ja/

Tuon F, Costa S. *Rhodotorula* infection. A systematic review of 128 cases from literatura. *Rev Iberoam Micol* 2008; 25: 135-140.

Urbina-Medina, H., & Lupi Acevedo, Y. A. (2022). Sepsis, bacteriemia y fungemia en pediatría. Conceptos actuales. *Gaceta Médica de Caracas*, 130. <https://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=03674762&AN=159945311&h=7n2Xlqvlkew7j3ufAR644nXHxlppqM4Yp%2Fs49BN5nD3427ZqStgAV4hT%2FNUkhRvae49tg%2Bj2RWJfeAh8ls6b2w%3D%3D&crl=c>

Vargas-Espíndola, L. A., Cuervo-Maldonado, S. I., Enciso-Olivera, J. L., Gómez-Rincón, J. C., Jiménez-Cetina, L., Sánchez-Pedraza, R., ... & Murillo-Sarmiento, B. A. (2023). Fungemia in Hospitalized Adult Patients with Hematological Malignancies: Epidemiology and Risk Factors. *Journal of Fungi*, 9(4), 400. <https://www.mdpi.com/2309-608X/9/4/400>

VILLAR, C. T., & APAC, C. M. G. CARACTERÍSTICAS EPIDEMIOLÓGICAS, CLÍNICAS Y DESENLACES DE LAS FUNGEMIAS POR *Cándida auris*, EN UN HOSPITAL DEL SEGURO SOCIAL DE LIMA-PERU, 2020–2022. https://repositorio.upch.edu.pe/bitstream/handle/20.500.12866/13662/Caracteristicas_TicllaVillar_Christian.pdf?sequence=1

Yu, J., Liu, X., Guo, D., Yang, W., Chen, X., Zou, G., ... & National China Hospital Invasive Fungal Surveillance Network (CHIF-NET). (2024). Antifungal susceptibility profile and local epidemiological cut-off values of *Yarrowia* (*Candida*) *lipolytica*: an emergent and rare opportunistic yeast. *Microbiology Spectrum*, 12(1), e03203-23.