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Systemic Candidiasis

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Abstract: ***Systemic candidiasis currently occupies one of the first places in medical mycology and infectious diseases. Whereas Candida albicans had previously been the dominant pathogen, this species now accounts for only half of the isolates detected in many surveys. The distinction between them is made taking into account their biological properties, manifested in the mycological analysis. Infections by Candida sp. have increased dramatically in recent decades. The development of new invasive techniques increases the risk in immunocompromised patients. The objective of this review is to present general aspects of systemic candidiasis.***

Keywords: Systemic Candidiasis, Candida Sp, Identification Tests, Antifungal Treatment.

1. INTRODUCTION

Candida is the main agent responsible for mycosis. The disease caused by this microorganism is very broad, ranging from mucocutaneous infection in healthy patients to severe invasive disease in patients with risk factors. The importance of invasive candidiasis is due to its high frequency and high mortality [1, 2].

Candidemia is defined as the isolation of any species of Candida in at least one blood culture sample and the association of generalized or focalized clinical manifestations suggestive of this entity. There must be a high suspicion in the presence of known risk factors and evidence of Candida isolation in any sterile biological fluid [3, 4].

Although Candida albicans continues to be the most frequent species, the emergence of C. parapsilosis is observed, which has become an important opportunistic pathogen. Infection by C. parapsilosis is associated to a greater extent with horizontal transmission, which is why outbreaks of invasive candidiasis by this species have been reported in ICUs, secondary to

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transmission by the hands of staff. This increase is associated with the use of vascular catheters, parenteral nutrition, neoplasia, neutropenia, and previous exposure to azoles [5, 6]. The distinction between them is made taking into account their biological properties, manifested in the mycological analysis (appearance of the colonies, fermentation of different sugars and growth in certain culture media [7, 8].

Currently, Candida infections are an important cause of healthcare-associated infection, due to advances in medical techniques and the increase in pediatric patients at risk of acquiring invasive fungal infections [9].Among the main risk factors are invasive techniques (central catheters, intubation, parenteral nutrition, abdominal surgery) and the administration of broad-spectrum antibiotic therapy [7].

In recent decades, fungal infections have been considered a growing process of global concern. Candida species rank fourth among the most common microorganisms isolated from blood cultures in the United States and fifth in Spain as the etiologic agent of sepsis. C. albicans causes 60% of candidemia followed by C. parapsilosis (20%) and C. tropicalis (7%) [10]- [15].The objective of this review is to present general aspects of systemic candidiasis.

Development

Candidiasis

Definition

It is a primary or secondary infection, caused by yeasts of the genus Candida, with extremely variable clinical manifestations, of acute, subacute or chronic evolution, in which the fungus can cause cutaneous, mucocutaneous, deep or disseminated lesions [8], [12].

Etiological agent

They are yeasts of the genus Candida that are part of the normal microbiota of the skin and mucous membranes (mouth, vagina, upper respiratory tract, gastrointestinal tract) of mammals. This genus includes approximately 150 identified species, whose main characteristic is the absence of a sexual form. The main agent is C. albicans; other species may be involved such as: C. tropicalis, C. famata, C. krusei, C. lusitaniae, C. parapsilosis, C. dubliniensis, C. pseudotropicalis, C. zeylanoides and C. guilliermondii [16], [17].

Epidemiology

It is a cosmopolitan infection. It is considered one of the most common opportunistic infections in humans. Its incidence has increased considerably in the last 20 years. Yeasts are the cause of 7.45% of mycoses, 25% of superficial mycoses and between 75 and 88% of nosocomial fungal infections. The geographical distribution of this mycosis is universal and more than 70% of them are produced by C. albicans. Yeasts of the genus Candida exist in nature, in the soil and fresh water, vegetables, fruits, exudate from trees, grains and in general any substance rich in simple carbohydrates. They are habitual inhabitants of the digestive, respiratory and mucocutaneous regions of humans and domestic animals [18], [19].
Normal skin may also harbor resident yeast microbiota, including C. parapsilosis, C. guilliermondii, C. krusei; but C. albicans and C. tropicalis are not regularly found on normal skin, except in the anogenital region and around the mouth. C. albicans can be isolated from

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normal vaginal mucosa and, less frequently, C. tropicalis, C. parapsilosis and C. krusei [8], [16]. Superficial candidiasis is frequent, easy to treat and does not threaten the patient's life, while systemic candidiasis with an acute or chronic evolution is generally serious. Most of these infections originate from an endogenous focus (gastrointestinal or respiratory tract) although the participation of external sources is not ruled out [19].

Routes of infection

Most infections are endogenous, originated from mucocutaneous or cutaneous reservoirs introduced by catheters or other devices for medical use, which interrupt the skin barrier. They can be exogenous, for example in hospitals, where yeasts can be transmitted to infants, transplant patients or immunosuppressed patients, through surgical materials, dialysis equipment or poorly decontaminated endoscopes, and through horizontal transmission of yeast infections on the hands or nails of personnel who works in ICUs without proper protection [20], [21].

Predisposing factors

The predisposing causes can be grouped into:
Local: maceration, contact with water, poor hygiene.
Physiological: pregnancy, extreme ages.
Endocrine: diabetes mellitus, hypothyroidism and other endocrinopathies.
Alteration of the normal flora: due to the use of antibiotics.
Hematological diseases: lymphomas, leukemias, aplastic anemia, neutropenia, hypo and aganmaglobulinemia, agranulocytosis.
Iatrogenic factors: prolonged use of corticosteroids, chemotherapy drugs, immunosuppressants, cytotoxic agents, parenteral nutrition, transplants, abdominal surgery, use of probes and catheters, radiotherapy, prostheses, hemodialysis.
Debilitating diseases: neoplasms, AIDS, starvation, severe and extensive burns, drug addiction, tuberculosis and other infectious diseases [19], [22].

Pathogenicity factors

1- Adhesion capacity of yeasts to different surfaces: it is a strong interaction between a yeast adhesin and a host cell receptor.
2- Production of extracellular enzymes: they are proteinases and phospholipases specific to each strain. A family of 10 isoenzymes with proteinase activity, known as Sap (secreted aspartic proteinase), have been detected in C. albicans, of which Sap 1-3 are crucial for superficial infection and Sap 4-6 would be important in invasive candidiasis [22].
3- Production of hyphae and pseudohyphae: increases the invasive capacity of the yeast, the adherence capacity, the resistance to phagocytosis and the power to damage the host cells.
4- "Switching" or phenotypic and antigenic variability: it is a spontaneous, frequent and reversible change between different phenotypes distinguishable by the morphology of the colony or by cell morphology [20], [21].

Host defense mechanisms

Non-immune:

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- Interaction with other members of the microbial flora.
- The functional integrity of the stratum corneum.
- The desquamation process due to epidermal proliferation induced by inflammation.

Immune: Humoral and cell-mediated immunity [22].

Candidemia

Candidemia it consists of the finding of the fungus in blood cultures of hosts that do not present immunological changes or demonstrable visceral compromise, it can be transient if it is isolated in a single blood culture and persistent if it is isolated in several blood cultures. In most cases, the elimination of the fungus is obtained by removing the catheter and if the patient does not have associated immunosuppression factors, it is not necessary to indicate systemic antifungals. Candidemia in neutropenic patients should always be considered as a potentially serious systemic infection, the risk of death is high and laboratory procedures for diagnosis are slow, and specific treatment should be indicated in all cases. It is more frequent in patients with malignant hematological diseases and in those who present conditions or surgical interventions of the gastrointestinal tract [8], [23].

Laboratory diagnosis samples

- Skin scales and faneras, Mucosal swab: buccal, vaginal and balano-preputial groove, Fecal matter, Blood culture, Sputum, Biopsy, CSF, Hepatic puncture. (Take into account the previous recommendations, the sampling and the storage conditions thereof) [18], [22].

Fresh microscopic examination

If it is horny material (skin flakes, nail scrapings, hair) it is examined with a 10% potassium hydroxide (KOH) solution (to break up and clarify the material). In the case of material obtained from mucous membranes and feces, the material is examined directly between slides and coverslips. Also in both cases the Giemsa staining technique can be used. If it is sputum, bronchial washing/brushing and/or macerated tissue fragments, it is convenient to observe the material with 10% KOH. If the fungus is present in the sample, yeast-like elements of 3 to 5µ in diameter and pseudohyphae are observed [16], [26]. Gram-stained smears of the above biologics. In this technique, single or budding gram-positive yeasts (blastoconidia) can be appreciated with or without the presence of pseudomycelium. The pathogenic role of Candida is given greater validity when more than four yeasts per field are appreciated, when they are observed at 400x magnification with or without pseudomycelium or true hyphae [24]-[26].

Culture

The development of the yeasts becomes visible after 24 - 48 hours at room temperature, although it is not convenient to eliminate the seeded tubes before 7 days for the superficial materials, and one month for the deep ones. The colonies obtained are generally smooth, soft, shiny, white or slightly beige in color; with time they can become rough, folded or membranous, with entire borders, limited and slightly elevated. On microscopic examination, multiple yeasts, round or oval, single or budding, are observed. Fungi of the genus Candida grow well on general media: Sabouraud glucose agar (ASG), Czapek, potato dextrose agar (APD). It is advisable to sow in media with antibiotics to inhibit bacterial growth (Sabouraud agar with chloramphenicol) and with cycloheximide (Mycosel) to inhibit the development of

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contaminating fungi. It is necessary to take into account that C. krusei, C. tropicalis, C. parapsilosis and C. zeylanoides are sensitive to this product [12], [16].

Identification

Fungi Yeast identification can be carried out according to four different criteria: morphological, biochemical, immunological and genetic. Morphological criteria can be macroscopic and microscopic. The macroscopic criteria take into account the characteristics of yeast colonies growing on culture media: white, creamy colonies with a yeasty odor that become wrinkled, opaque colonies with age, do not develop aerial mycelium but spider-like processes may appear on the periphery of the colonies, if a defined aerial mycelium is observed, the possibility should be considered that it is a dimorphic fungus or yeasts that can form true mycelium such as Geotrichum, Galactomyces, Trichosporon or Blastoschizomyces, the orange-red colonies, creamy in appearance are characteristic of the genus Rhodotorula and Sporobolomyces. The most commonly used microscopic criteria are: morphology, germ tube test or early filamentation, the formation of hyphae, blastoconidia, chlamydospores and arthrospores. Microscopic examination reveals spherical or ovoid unicellular microorganisms, with thin walls, 2 to 4 µm in diameter, budding, with little or no pseudomycelium or mycelium [26],[27]. The germ tube test, is used for its speed in presumptive identification and because it can be performed in all microbiology laboratories. Rare germ tube forms have been described in C. tropicalis and C. dubliniensis phenotypically similar to those produced by C. albicans. The germ tube is a filamentous extension of the yeast cell, without taper at its origin, usually half as wide as the parent cell and four times as long as the parent cell. Only C. albicans and to a lesser extent C. dubliniensis are capable of producing true germ tubes in two and a half to three hours, C. tropicalis can produce early pseudohyphae similar in appearance to germ tubes but with a characteristic constriction zone adjacent to them. The mother cell, in other species it can be developed, but in later stages. The procedure consists of inoculating the strain under study on cornmeal agar plus Tween 80, at a final concentration of 0.02% to reduce surface tension and increase the formation of hyphae and blastoconidia; its presence suggests that the yeast to be identified belongs to some species of the genus Candida [12], [16], [18], [26], [27].

Biochemical and enzymatic criteria

Identification based on nutrient assimilation methods Wickerham described a broth assimilation and fermentation method for yeast identification, through the ability to use a substrate as either the sole carbon source or the sole nitrogen source. The medium is not commercialized and must be made by hand [12], [16].

Conventional auxonogram

Test based on the separate application of different hydrocarbon or nitrogenous nutrients, on a synthetic base medium to observe the selective growth of a yeast near the nutrients necessary for its development, aqueous solutions sterilized by filtration are used, Oxford cylinders in wells made on agar or absorbent paper discs soaked with the nutrient; All known alcohols and sugars can be used as a carbon source and peptone, asparagine, urea, ammonium sulfate, potassium nitrate and various amino acids as a nitrogen source [26], [27].

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Carbohydrate fermentation studies (zymogram)
From a 24-48 hour culture of the yeast, prepare a suspension in 2 milliliters (mL) of sterile distilled water, equivalent to McFarland's number two turbidity standard. With a sterile pipette, add 0.2 mL of this suspension to each of the tubes containing the carbohydrates to be studied in a Durham tube and shake them slightly. Inoculate a tube without sugar that will be used as a control, incubate at 30°C and visualize daily for up to one week. Only the presence of gas in the Durham tube is interpreted as a positive test. Many specialists use a pH indicator in the fermentation medium. A color change in an inoculated tube is an indicator that the sugar is assimilated. Any carbohydrate that is fermented is also assimilated, the opposite is not necessarily true [27].

Pathological studies
Cytology and histopathology can demonstrate parasitic elements: single round or oval yeasts or with blastoconidia, with or without pseudomycelium formation. In addition to hematoxylin-eosin staining, the use of Papanicolaou and silver stains (Gomori, Grocott or Gridley) is recommended [12], [16].

Semi-automated trading methods
There are semi-automated commercial methods based on the assimilation of nutrients, among which are the Auxacolor gallery (Bio-Rad), the Uni-Yeast Tek system (Remel), API 20 C AUX (bioMérieux), the latter consisting of a gallery of 20 domes with dehydrated substrates that allow 19 assimilation tests to be carried out; allows the identification of 34 different species through the Analytical Catalog or the Computer Identification Program supplied by the manufacturer [28]. Other semi-automated systems that are based on nutrient assimilation are the ID 32 C gallery (bioMérieux) and the Vitek system (bioMérieux). The Vitek 2 system (bioMérieux), the Biolog YT MicroPlate system (Biolog) and the Rapid Yeast Identification Panel MicroScan (Dade Behring) are fully automated systems that allow the identification of multiple yeast species belonging to different genera [25], [29], [30].

Automated methods
The development of MALDI-TOF MS (matrix assisted laser desorption ionization-time of flight-mass spectrometry) technology more than 30 years ago has allowed the use of mass spectrometry in routine microbiological diagnosis. It allows the identification of microorganisms through the analysis of proteins, mainly ribosomal, from colonies or directly from samples through the creation of a mass spectrum that is specific for each species[5], [31], [32].

Chromogenic media
Several different media are commercially available such as CHROMagar Candida, Colorex Candida® (Biomedics), Cromogen Albicans (Biomedics), Candida ID (bioMérieux), Albicans ID2 (bioMérieux), Candida ID2 (bioMérieux). In Cuba, the Chromium CND-C medium from BIOCEN-CUBA, of national production, is marketed. All have as a common denominator the hydrolysis of the chromogenic substrate present that determines a specific color change for the yeast under study. After using these media, some authors recommend additional phenotypic tests to confirm the species and the use of chromogenic culture media

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(BIGGY/Nickerson agar, Pagano-Levine agar, CROMO AGARCandida® and CANDI-SELECT®) [8], [22], [33].

Immunological tests

The intradermal reaction with candidin is most useful in the clinical follow-up of the patient and its prognosis. There is a large percentage of people who test positive for the Candida commensal role. Serologic tests are used in systemic and granulomatous candidiasis. These rapid diagnostic methods are based on the specificity of the antigen-antibody reaction observed by the agglutination of latex particles using monoclonal antibodies for different species of Candida. Several brands can be found on the market such as Bichro-latex albicans (Fumouze), Krusei-color (Fumouze), Bichro-Dubli® (Fumouze) among others. The Platelia™ Candida Immunoenzymatic Assay is available on the market with very good sensitivity and specificity that identifies circulating manana-antigen of Candida spp., or antibodies against these mananas [34] - [36].

2. MOLECULAR METHODS

They allow to recognize those organisms whose phenotypic characteristics make them difficult to differentiate from other fungi by conventional methods. Among the most widely used molecular methods currently for the identification of yeasts are different polymerase chain reaction (PCR) techniques: real-time PCR (LCCandida Kit M, Roche Diagnostics, Meylan, France), multiple PCR for the detection of infections by different species, PCR nested, in situ hybridization, among others [37], [38].

In vitro yeast antifungal susceptibility tests

In 1992 the National Committee for Clinical Laboratory Standards, currently the Clinical Laboratory Standards Institute (CLSI) in the USA, developed the first international standard for yeast susceptibility. This document (M27-A) allowed to measure the in vitro minimum inhibitory concentrations (MIC) of the main opportunistic yeast species. Two standards are currently available that use the broth microdilution method for this purpose. One is the CLSI document (M27-A3), which has established cut-off points to define in vitro susceptibility to certain antifungals such as azoles, and the other is the European standard, Subcommittee on Antifungal Susceptibility Testing (AFST) of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), EDef 7.2 document that has been shown to be equivalent to the CLSI standard in non-fermenting yeasts [29], [30]. The disk diffusion method, standardized by CLSI document M44-A for Candida spp. shows an inhibition halo whose measurement correlates with the reference method [39]. There are other commercial methods, one of the most used is the Etest (AB BioDisk, Soina, Sweden), for in vitro susceptibility of Candida spp. against Fluconazole and Itraconazole. Other alternatives are: ATB Fungus 3 panel and Sensitive Yeast One 3 (Trek Diagnostic Systems and East Grinstead) [30], [39] - [41].

Treatment

If the patient has any risk factors for severe infection (metastatic infection, sepsis with hemodynamic instability, neutropenia) and/or risk factors for infection by fluconazole-

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resistant Candida species, the use of an echinocandin or amphotericin B liposomal as an alternative will be chosen. Patients with no risk factors, non-neutropenic, or neutropenic patients who are not severely ill can receive fluconazole. Subsequently, and in all cases, the treatment will be adapted according to the fungigram and, whenever possible, treatment with fluconazole will be continued. Treatment should be maintained until the symptoms resolve and the fever disappears and at least until 14 days after the first blood culture without fungal growth. During treatment, control blood cultures should be performed every 2 or 3 days until they are negative. After discontinuation of treatment and during the subsequent 3 months, evolution must be monitored and a high index of suspicion maintained, investigating possible recurrences in the event of a new febrile episode in a susceptible patient [2].

Empirical treatment

Empirical treatment should be started in patients with neutropenia and persistent fever for more than 5 days. It is considered in critically ill patients in whom no other cause can be found to explain the fever, and in the presence of serological markers of candidemia [1], [2].

Treatment in the non-neutropenic patient

The recommended treatment in the case of suspected candidemia in a non-neutropenic patient is fluconazole or an echinocandin. An echinocandin should be chosen first if the patient has recently received azoles, in patients with moderate or severe disease, in patients with hemodynamic instability, or in patients at risk of C. krusei infection. Lipid amphotericin B is also another therapeutic option [2]

Treatment in the neutropenic patient

In neutropenic patients, the empirical therapy of choice will be liposomal amphotericin B, caspofungin, or voriconazole [3].

Vascular catheter management in the presence of candidemia, both in neutropenic and non-neutropenic patients, catheter removal is recommended. It is mandatory in both groups of patients in the following circumstances:

a) When it is demonstrated that the focus or origin of the candidemia is the infection of the endovascular catheter.
b) When there is phlebitis, cellulitis or signs of infection of the entrance door.
c) In case of shock or severe sepsis (once a new venous access is available).
d) When blood cultures with fungal growth persist 72 hours after the start of adequate treatment.
e) When the candidemia is caused by a species of Candida sensitive to the azole that the patient received as prophylaxis.
f) In candidemia by C. parapsilosis.
g) When there is endocarditis or risk factors for endocarditis (congenital heart disease, prosthetic valve and previous candidemia) [1]-[4].

3. CONCLUSIONS

Infections by Candida sp. have increased dramatically in recent decades. The development of new invasive techniques increases the risk in immunocompromised patients. What is really

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worrying is the lack of therapeutic options to deal with these diseases. We recommend research studies in the development of new antifungals and an updated control program, structured and applied at all levels of healthcare.

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