Risk factors and physiopathology of candidiasis

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Summary

Recent epidemiological surveys have demonstrated an important increase in nosocomial infections among which *Candida* sp. plays an increasingly prominent role. *Candida* is now involved in about 10% of all septicemia and leads to a very high mortality rate in immunodepressed patients. Clinical studies show that any modification of the host immune status can facilitate the proliferation of endogenous *Candida* which, according to the importance of the immune deficiency, can provoke diseases ranging from benign localized mucocutaneous candidosis to sometimes lethal systemic invasions. The pathogenic behavior of *Candida* cells is mainly due to a very high phenotypic biodiversity. Following even very slight environmental modifications, it may change its behavior through the appearance of new or amplified properties such as tube formation, adherence, protease secretion, etc. Together with the impairment of host defenses, these new invasive properties lead to the so-called opportunistic pathogenicity of *Candida* cells. From a host point of view, after the integrity of surface teguments, the mucosal protection is ensured by the Th1 "cellular" immune response which, through pro-inflammatory cytokine production, boosts the efficacy of the phagocytes (Polymorphonuclear cells and macrophages). Neutrophils are of particular importance as deep seated *Candida* proliferation is mostly associated with neutropenia. Whatever the pathogenic process, it is mostly due to modifications provoked by increasing medical awareness which makes patients more susceptible to illness. A better knowledge of the precise mechanisms involved and twould lead to improved strategies for prevention.

Key words

Candida, Candidiasis, Pathophysiology, Opportunistic disease, Epidemiology, Immune deficiency

Factores de riesgo y fisiopatología de la candidiasis

Resumen

Estudios epidemiológicos recientes han demostrado un importante aumento de las infecciones nosocomiales, entre las que *Candida* juega un papel cada vez más relevante. *Candida* se encuentra implicada en el 10% de las septicemias y provoca una mortalidad elevada en pacientes inmunosuprimidos. Los estudios clínicos muestran que cualquier modificación del estado inmunológico del huésped puede facilitar la proliferación endógena de *Candida* que, dependiendo del alcance de la inmunodeficiencia, puede provocar enfermedades que van desde candidiasis mucocutáneas localizadas benignas hasta invasiones sistémicas, en ocasiones letales. El comportamiento patógeno de *Candida* se debe principalmente a una biodiversidad fenotípica elevada. Incluso modificaciones ambientales mínimas pueden cambiar su comportamiento mediante la aparición de propiedades nuevas y amplificadas, como la formación de tubos germinales, la adhesión, la secreción de proteasa, etc. Estas nuevas propiedades invasivas unidas a la alteración de las defensas del huésped, provocan una patogenicidad oportunista de *Candida.* Desde el punto de vista del huésped, junto con la integridad de las barreras superficiales, la protección de las mucosas está asegurada por la respuesta inmune celular de tipo Th1 que, a través de la producción de citocinas pro-inflamatorias, mejora la eficacia de los fagocitos (células polimorfonucleares y macrófagos). Los neutrófilos son particularmente importantes ya que la proliferación de *Candida* en los tejidos está principalmente asociada con la neutropenia. Cualquiera que sea el proceso patogénico, éste se debe fundamentalmente a las modificaciones asociadas con los avances médicos que hace a los pacientes más susceptibles. Un mejor conocimiento de los mecanismos concretos de patogenicidad implicados debería orientarnos a mejorar las estrategias de prevención.

Palabras clave

Candida, Candidiasis, Patofisiología, Infección oportunista, Epidemiología, Inmunodeficiencia

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Multidisciplinary approaches to the physio-pathology of candidiasis has produced some new insights.

Three levels of investigation may now be usefully considered :

(i) Epidemiological surveys: this aspect of the relationship between candidal and human populations gives the real importance of the disease in terms of not only quantity but also in terms of evolutivity. Increasingly accurate epidemiological surveys have produced numerous results leading to a better understanding of the multifactorial aspect of candidiasis and to an improved evaluation of prognosis.

(ii) Clinical aspects of candidiasis: increase in medical awareness has led to the identification of new diseases and nosocomial infections among which candidiasis is prominent. Defense impairments provoked by sophisticated therapies and many other iatrogenic comportments are unfortunately taken advantage of by various opportunistic diseases.

(iii) Cellular and molecular biology: recent developments in these fields provide considerable insight into these phenomena. The genetic and phenotypic variability of the *Candida* cell is better understood and the comprehension of the many mechanisms, cells and molecules involved in the immunological discrimination processes of the human host increases day by day.

The physiopathology of candidiasis requires that all these findings be considered within a dynamic context, whatever the epidemiological, clinical, cellular or molecular levels encompassed.

EPIDEMIOLOGICAL FACTORS

From January 1980 through April 1990, 27,200 fungal isolates causing nosocomial infections were reported from 180 hospitals participating in the US National Nosocomial Infections Surveillance (NNIS) system; *Candida* species accounted for 19,621 (72.1%) of these isolates; the rate of candidal bloodstream infection has increased by as much as 487% throughout this decade [1,2]. Other epidemiological surveys note an 11-fold increase during the same period [3]. The incidence of deep-seated mycoses in the northern hemisphere is estimated to be 600 mycosis situations per million population per year [4]. *Candida* sp. jumped from the 8th to the 4th place in septicemia during the period 1984-88 and corresponds to more than 10% of nosocomial septicemia [5].

Thirty-seven reports, published between 1952 and 1992 describing 1,591 cases of systemic *Candida* infections among patients with cancer, showed that species other than *Candida albicans* accounted for 46% of all systemic infections; in particular, *Candida tropicalis* accounted for 25%, *Candida glabrata* for 8%, *Candida parapsilosis* for 7% and *Candida krusei* for 4% [6]. Emerging pathogens such as *Malassezia furfur; Trichosporon beigelii, Rhodotorula* species, *Hansenula anomala, Candida lusitaniae,* were also observed. Organisms once considered environmental contaminants or only industrially important, such as *Candida utilis* and *Candida lipolytica*, have now been implicated as agents of fungemia, onychomycosis, and systemic diseases.

The noticeable increase in *Candida* infection in immuno-compromised patients occurs with a very high mortality rate which sometime reaches 50% [7-9].

According to their variable susceptibility to antifungal agents [10,11], the time needed for an accurate identification, and the life-threatening infections provoked, these new pathogens, which are mainly of iatrogenic origin, increase the burden of clinical mycology [12,13].

Another important point concerns the origin of the pathogenic strains. For a long time the endogenous commensal situation of the fungus was considered to be the essential source of contamination. Development of accurate DNA typing methods shows that nosocomial yeast infections can sometimes behave like minor epidemics resulting from the selection of more virulent strains [14-17].

FROM A CLINICAL POINT OF VIEW

Candida albicans may be considered as a commensal of the normal flora of the digestive tract. Pathogenicity results essentially from modifications of the host defense mechanisms which secondarily initiate transformations in the fungal behaviour.

The pathogenic behaviour of *Candida* may appear following even a slight modification of the host. Mucocutaneous candidiasis has been observed in people with physiological cellular immune deficiencies. Thrush in the newborn or the elderly may be related to an inefficiency of the thymus. *Candida* vulvovaginitis associated with pregnancy or use of contraceptives may be linked to the role of progesterone on T-cells and on PMN anti-candidal activity [18-19]. *C. albicans* possesses an oestrogen-binding protein that links to oestrogens with high affinity and specificity [20]. Moreover, human chorionic gonadotropin (hCG), human luteinizing hormone (hLH), and other CG-like proteins induce the transition of *C. albicans* from the blastospore to the hyphal form [21]. Moreover, clinical information dating back many years suggests that Th1 responses are weakened systematically during pregnancy.

Stress is an often forgotten cause of temporary immunodeficiency. Neuroendocrine regulation and chronobiological effects may notably modulate the immune system and provide the opportunity of fungal proliferation [22].

As Wilson (1962) put it:"*C. albicans* is a better clinician and can discover abnormalities in persons much earlier in the course of the development of such abnormalities than we can with our chemical tests".

In addition to physiological modifications, there is a long list of diseases that may facilitate the development of opportunistic pathogens. Primary or secondary deficits affecting myeloid or lymphoid lineages show the fundamental role of these cells in the control of self-discrimination and homeostasis. Neutropenia and its duration is obviously one of the main causes of systemic *Candida*-proliferation [23-25], since mucocutaneous candidiasis is directly related to T-cell deficiencies. Diabetes and other endocrinopathies are also sources of mucocutaneous candidiasis [26,27].

The considerable increase of *Candida* infections over the last decade, is certainly linked to the development of new drugs and techniques which allow the physician to penetrate deeper into the tissular, cellular and molecular intimacy of patients thus opening breaches for *Candida* to invade. These so-called iatrogenic factors involve new chemical and physical therapeutic techniques such as:

- Antibiotherapy, particularly poly-antibiotherapy causes modifications of the mucosal flora leading to proliferation of *Candida* cells [28-31].

- Corticotherapy, directly [32] or through modification of the cytokine network [33] may affect polymorphonulear (PMN) [34], macrophage [35] and T cell activity leading to an impairment of their antifungal activity

[36,37].

- Chemotherapy leading to depletion of leucocytes provides a breakthrough which facilitates fungal infections [38,39]. Moreover chemotherapy may alter PMN function [40] and ulcerate digestive mucosa contributing to proliferation of *Candida* cells [41,42]; these phenomena may be potentiated by anti-acid treatments [43].

- Surgery, principally of the gastro intestinal tract, associated with chemical, physical and psychological stresses favors fungal development [44].

- Catheterism may provoke an injury of the teguments, and also provide a substrate which, once within the blood, is quickly covered by fibronectin, fibrinogen, platelets and other plasma components ; it constitutes a support for settlement and proliferation of microorganisms which are, at this level, more resistant to antibiotics and to antifungal agents [45-48].

- Transplantation by itself integrates all iatrogenic factors [49,50].

Most of these iatrogenic factors are related to an impairment of the surface integrity and immune defenses. Increased medical awareness may explain the expanding rate of these diseases as well as the transformation of the spectrum of nococomial pathogens.

CELLULAR AND MOLECULAR ASPECTS

As a diploid eukaryotic cell *Candida* obviously possesses enough genomic resources to cope with many kinds of environment. From a very simple culture medium providing basic carbon and nitrogen sources at room temperature through to the complexity of the human body, *Candida* is capable of growing, mutiplying and colonizing. Devoid of sexual reproduction, *C. albicans* can face the numerous environmental selection factors by important phenotype and karyotype variations, the latest being mainly translocation, chromosome fragmentation and aneuploidy. Karyotype analysis has gained in interest since the methodologies now used offer greater discrimination. However, until recently, their main use has been epidemiologic since it is difficult to establish obvious links between karyotypes and phenotypes. Gene cloning, gene disruption, gene mapping and other molecular genetic techniques have yielded considerable information in the past few years and should certainly prove helpful for the comprehension of the molecular mechanisms involved in candidal variability and virulence.

At the cellular and molecular level, the "commensal" *Candida*, adopting pathogenic behaviour has to switch from a quiet way of life to a more complicated one to overcome the numerous barriers naturally developed by the host. It has to go through many steps to colonize and to proliferate through what is a usually well protected citadel. Decrease in host defenses is not sufficient to explain invasion, since a particular strategy is needed for the fungus to be able to penetrate and grow within the host tissues. In the following sections we describe first the fungal strategy for invading the host tissues and secondly, the main defense mechanisms that the host could develop in order to cope with the intruder and stop the invasion process.

A. FUNGAL STRATEGY

To switch from a saprophytic to a pathogenic behaviour, *Candida* has to develop some phenotypic characteristics which allow penetration into the host organism. The propensity of the fungal cell to change its behaviour is very great and depends on its surroundings [51]; it has been shown that phenotypic switching in strains of *C. albicans* is associated with invasive infections [52,53]. To be successful as a pathogen *Candida* has to overcome two main obstacles: adhesion to host constituents and production of lytic enzymes. It is now well established that these two processes are associated with morphological variations. By operating a dimorphic transition [54,55] from the blastospore to the filamentous stage, *C. albicans* increases its adhesive properties and proteinase secretion. Many studies have shown the capacity of *Candida* cells, particularly the hyphal form, to bind to epithelial mono- or di-saccharides by means of lectin-like surface components [56-60]. Many other fungal components were found to be involved in the linkage to epithelial cells [61-65]. In contrast, fixation to the endothelial layers requires protein-protein interactions [59,66] and may need the participation of platelets [67]. Adherence of the fungal elements to endothelial cells is followed by the internalization of fungi by an active mechanism depending on endothelial cells and is associated with production of prostaglandins [68-71].

Numerous authors have reported the fixation of the fungus to the basement membrane or to extra-cellular matrix components:

- Fixation to fibronectin is mediated by a fungal 60 kDa multimer glycoprotein [72] which presents an antigen homology with integrins $\alpha 5 \beta 1$ and which recognizes an RGD sequence on the fibronectin molecule [73-75]. Strength of the binding increases with germ tubes and could involve interactions with different domains of fibronectin depending on the soluble or insoluble form of the molecule [76].

- Binding to laminin was shown to be mediated by a 60-68 kDa fungal mannoprotein with a quite high affinity constant [77,78]. Other linkages have been ascribed to collagen [79], entactin [80] suggesting multiple mechanisms for settlement and colonization.

The fixation capacity of *Candida* has also been demonstrated with respect to other host components :

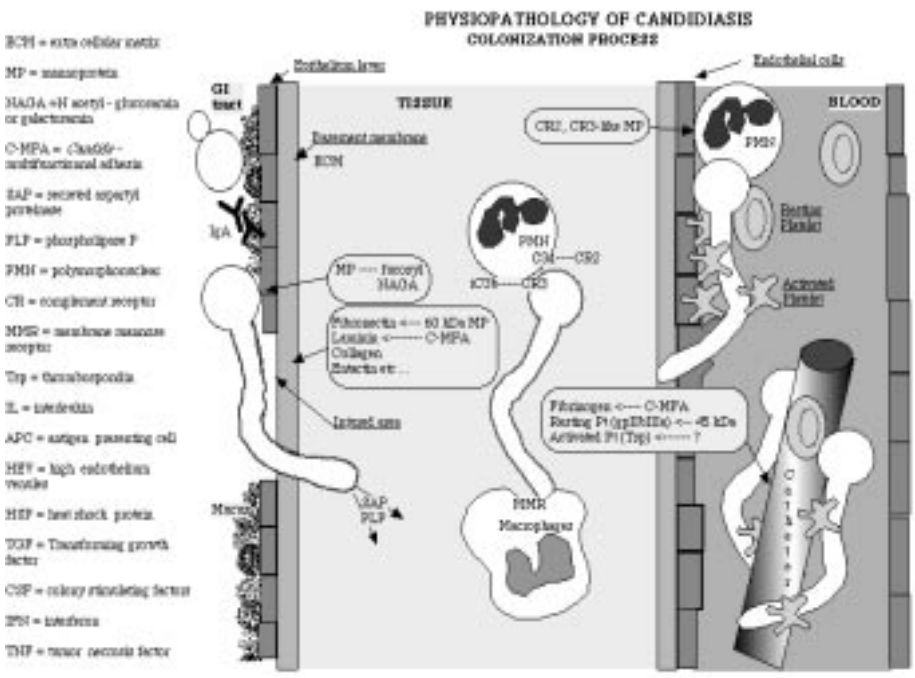
Two kinds of complement receptors were described. A CR3-like receptor showing homologies with the CR3 of mammal cells [81,82] capable of linking to iC3b fragments and which could also be involved in the binding to epithelial cells [83,65]. A CR2-like receptor binding to C3d [84,85], the expression of which is correlated to the pathogenicity of the tested *Candida* strains [86,87]. Whereas the CR3 has homologies with the integrin family, the CR2 seems to be linked to more eclectic adhesive components capable of binding to fibrinogen, laminin, and plastic surfaces as well.

Fixation to fibrinogen is mediated by fungal mannoproteins which, by means of cross-inhibition, have been shown to be the same as those involved in binding to laminin and C3d, suggesting the idea of a multi-functional adhesin of *Candida* (MFA-C) [88,89] [90-92]. Taking into account the multiple roles and the ubiquity of fibrinogen throughout the body, the possibility for *Candida* to bind to this molecule with high affinity should provide different strategies for the fungus to settle and even evade from immunological surveillance with a kind of mimicry by coating its surface with soluble fibrinogen molecules belonging to the host.

Fungal cells may adhere also on prosthetic devices introduced into the host, such as catheters, cardiac valves, dental prostheses and so on. As previously described the fixation of the fungus can be mediated by the numerous host components that are quickly coated onto the foreign devices. Moreover it has also been shown, in vitro, that *Candida* can link directly to plastic surfaces by using the

MFA-C [93]. *Candida* cells which constitute the biofilm coating synthetic devices are more resistant to antifungal drugs and provide a new niche for further spread [94,95].

Following attachment to host components, *Candida* cells need to secrete enzymes to penetrate deeper in the tissues. The secretion of aspartyl proteinases of *Candida* has been extensively studied and shown to be linked to the pathogenesis of the tested strains [96-105]. Other enzymes are also involved in the pathogenesis of *Candida* [106,107].



B. HOST-DEFENSE MECHANISMS

The possibility for the fungus to settle and proliferate depends on its surroundings which is, in the present case, the host organism. Facing the fungal invasive nature, there are numerous barriers and systems which are more or less interconnected, maintaining host integrity.

At the level of the mucosal surface, *Candida* cells share the locally available nutriments with other commensal organisms. Intact skin is well protected by keratinized cells. In the normal gastro-intestinal tract, fungal cells surrounded by mucins, secretory IgA and the numerous bacteria of the flora, multiply by budding and remain more or less quiescent. But it seems that, even a slight local surface modification can trigger the pathogenic process (see iatrogenic factors). The relationship with mucins [108,109] and the status of the mucosa are major factors in determining fungal behaviour [110].

Within the blood circulation *C. albicans* has been shown to be quickly surrounded by platelets which adhere, spread over the surface of the fungus and degranulate. In mice models they are rapidly, within ten to fifteen minutes, removed from the blood stream [111,112]. This mechanism may lead to the killing of the fungal elements by small peptides secreted by activated platelets, but it may also cause the fungus to fix endothelial layers with the help of the activated platelets leading to metastatic processes [67,113,114].

Endothelial cell invasion by *C. albicans* appears to stimulate the production and extracellular secretion of prostaglandins which are probably related to the modulation of the leukocyte response at the *Candida*-leukocyte-endothelial cell interface [68]. The resistance of endothelial cells to damage provoked by *C. albicans* is increased by IFN-γ [115].

Since the surface layers are altered or crossed, an inflammatory reaction occurs. The pivotal role in the defense mechanisms against *Candida* is played by the phagocytic cells: polymorphonuclear cells (PMN) and macrophages. PMN are the first cells to reach the fighting area within a few hours and actively cope with the invading cells. The considerable increase in candidiasis linked to neutropenia demonstrates the major role of this cell [23-25,116,117]. Anticandidal activity of granulocytopenic mice can be restored by SCF and G-CSF [118,119].

Recognition of the elements to be engulfed may be helped by opsonization mechanisms involving immunoglobulin Fc and complement receptors. Deficits in the adherence mechanisms are associated with high sensitivity to infection. PMN are very efficient because of their capability to phagocytize fungal cells and to produce lactoferrin and oxygen intermediates. Lactoferrin was demonstrated to have a high antifungal activity *in vitro* [120,121]; the oxydative burst and the numerous enzymes contained in the PMN granules are also responsible for the the killing of engulfed *Candida* cells [122,123]. Moreover, death of the PMN in the abcess area is followed by the release of a PMN-fungistatic 30 kDa protein [124]. Macrophages reach the inflammatory area secondarily. The adherence to fungal cells can also be mediated by a membrane mannose receptor [125], by means of vitronectin [126] or other receptors [127]. The fungistatic or fungicidal activity of macrophages is more often correlated to the production of nitrogen monoxyde (NO) than to that of oxygen radicals [128-130].

Migration of the phagocytic cells, activation of their metabolism and particularly the oxydative burst, increased expression of membrane receptors (FcRs, CRs) benefit largely from the local secretion of inflammatory cytokines and particularly IFNs and TNFs [131-134] which in turn, can be modulated by *Candida* components [135-137]. Other cytokines are also involved in these mechanisms: IL-2 [138], IL-8 [139], GM-CSF [140].

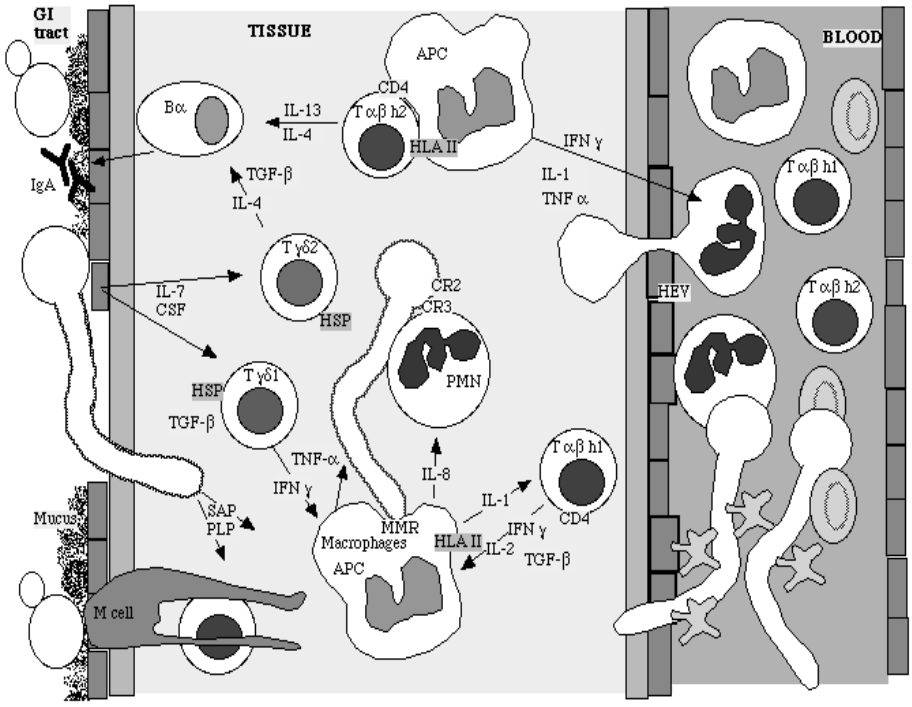
The local level of cytokines is largely dependent on the antigen specific recognition operated by T lymphocytes. Two different subsets of T helper cells were described (Th1 and Th2) and shown to play antagonistic roles. Th1 is associated with IFN-γ, IL-2 production and Th2 with IL-4 and IL-10 mainly. Th1 corresponds to what has long been designated as cellular immunity while Th2 controls the humoral response. By means of experimental murine models, it was demonstrated that protection against mucocutaneous candidiasis is associated with a Th1 response and in contrast the disease was linked to a Th2 reactivity [141]. Activation of Th1 rather than Th2 may depend on various factors, such as the antigen presenting cell, the HLA II molecules involved, the presence

of particular cytokines and also the steric configuration of the antigen. Artificial protein conjugated mannan can direct a Th1 response when obtained in oxidizing conditions and a Th2 response when conjugated under reducing conditions [142]. These results present considerable interest regarding the possibility of driving the immune reactivity toward an efficient response [143]. However the correlation between the local immune response and the general immune status is difficult to establish and results remain controversial [144,145].

The protective role of humoral antibodies in the resolution of systemic candidiasis is not well established. Despite results showing the increase of anti-enolase antibodies [146] and anti-*C. albicans* heat shock protein (HSP) 90 [147] in patients recovering from systemic candidiasis, there is no clear correlation between humoral immunity and resistance or susceptibility to infection with *C. albicans* [148]. Nevertheless, at the mucosal level, IgA secretion could be involved in the local protection [149-151].

HSP also called "chaperones" are highly conserved throughout species evolution [152] suggesting their major role in cell biology. Candidal HSP 90, which appears to be a major antigen in *Candida* infections, shares common epitopes with human HSP, leading to possible interferences between self and non-self reactivity [147]. Other HSP were described in *Candida* [153,154]. HSP are mainly involved in repair and refolding of denatured proteins and could be also involved in antigen processing. They are supposed to intervene in the antigen recognition of the T (CD4-/CD8-) γδ cells. Taking into account this property, the location of T γδ cells in the subepithelial area and the fact that they are able to produce large amounts of IFN-γ, it could be hypothetized that they play an important role in the modulation of local inflammatory reaction [155,156] and deserve to be further studied in candidiasis.

CYTOKINE INTERPLAY



CONCLUSION

In the context of immunodeficient hosts, *Candida* may behave as a true pathogen and proliferate until confronted by an efficient defense mechanism. The balance is dynamic with, on one hand the multiple barriers of host immunity, and on the other the burden of the invading cells. Recent progress in the understanding of the cellular and molecular mechanisms involved in mucocutaneous candidiasis raises hopes of possible control of the immune response. Considering that about one-third of immunosuppressed patients affected by *Candida* septicemia die, and taking into account the fact that iatrogenic factors lead to the selection of more pathogenic strains and to the emergence of species resistant to fungal therapies, the best medical attitude is obviously to survey and prevent a possible extension of *Candida* cells of endogenous or exogenous origin.

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