

CANDIDA AND HUMAN DISEASE

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SUMMARY: A general review on candida and human disease emphasizing Candida Species, clinical manifestations, immune response NK failure and immunotherapy.

Key-words: Candida - Candidiasis - Allergy.

Candidiasis is the disease caused by fungi of the genus *Candida* which is a common saprofit.

CANDIDA SPECIES

Candidiasis is clinically mainly linked to *Candida albicans* but on the last few years other *Candida* species have been found in human disease particularly in immuno compromised hosts (Benett, Ellis, Lehman, Lehner 1993, Lewis, Patterson, Shoham). Therefore nowadays several species of *Candida* may be etiological agents not only *Candida albicans* but also *C. tropicalis*, *C. Krusei*, *C. parapsilosis*, *C. guilliermondi*, *C. kefyr*, *C. pseudotropicalis* (*Torulopsis*) *glabrata*, *C. dubliniensis* and *C. lusitaniae*. All are ubiquitous and occur naturally on humans, especially *C. albicans* which is currently a commensal of the gastro-intestinal tract (Ashman, Benett, Ellis, Shoham).

■ **Candida (*Torulopsis*) *glabrata*:** *Candida glabrata* is one of the most common yeasts to be found on body surface and is often isolated as an incidental finding from the skin, the urine and the faeces. It has been implicated as an opportunistic agent in systemic and superficial infections especially in immunocompromised hosts and isolated from patients with septicemia, pulmonary infections, endocarditis and pyelonephritis, *Candida glabrata* do not present hyphae in microscopic appearance (Ellis).

■ **Candida (*Torulopsis*) *Fumata*:** *Candida* (*Torulopsis*) *fumata* is a common environmental host but scarcely

recovered from human specimens mainly from skin. It doesn't produce pseudohyphae (Ellis).

■ **Candida (*Torulopsis*) *haemulonii*:** *Candida haemulonii* has been isolated from a few human cases but clinical relevance is scarce (Ellis).

■ **Candida *Tropicalis*:** *Candida tropicalis* is a cause of major clinical concern particularly in immuno compromised hosts. It could become a source of septicemia and disseminated Candidiasis especially in patients with AIDS, diabetes, leukemia, lymphoma or submitted to therapeutic immunosuppression. It is the second most frequent encountered medical pathogen after *Candida albicans* and it can also be found as a commensal in normal human mucocutaneous flora. It could be found in environment as well as food (shrimps, kefir) as in soil (Ellis, Shoham).

■ **Candida *kefyr* (*Pseudotropicalis*):** *Candida kefyr* is a rare cause of Candidiasis and usually associated with superficial cutaneous manifestations rather than systemic disease. *Candida kefyr* has been obtained from lung infections, skin and nails and also from food, as cheese and dairy products (Ellis).

■ **Candida *krusei*:** *Candida krusei* is usually associated with some forms of diarrhea in children and in some cases with systemic disease. It can colonize the gastrointestinal, respiratory and urinary tracts and skin of immunocompromised patients. It can be isolated from food and beverage (beer, dairy products), animals, birds and faeces. (Ellis).

■ **Candida (*Torulopsis*) *norvegiensis*:** *Candida norvegiensis* is very rare on clinical mycology but it can cause peritonitis and disseminated Candidiasis (Ellis).

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■ **Candida parapsilosis:** *Candida parapsilosis* is an opportunistic human pathogen which may cause either systemic disease, endocarditis and cutaneous infections especially of the nails. It has been also related to endophthalmitis and fungemic *Candidal* septicemia (Ellis). Environmental isolations have been obtained from sea waters, meats, olives and faeces (Ellis).

■ **Candida viswanathini:** *Candida viswanathini* is a very rare finding in clinics (Ellis).

■ **Candida lusitanae:** *Candida lusitanae* has been isolated from several cases of disseminated Candidiasis, septicemia and pyelonephritis. It can also colonize the gastrointestinal, respiratory and urinary tracts (Ellis). Environmental identification has been obtained from corn-meal, citrus peel, fruit juices and milk from cows with mastitis (Benett, Ellis, Shoham, Yoon).

■ **Candida guilliermondii:** *Candida guilliermondii* has been isolated from numerous human infections mainly from the skin. Systemic infections are rare. *C. guilliermondii* can be also found in normal skin faeces or animals products (wasps, buttermilk, leather, fish, beer and sea water) (Ellis).

■ **Candida dubliniensis:** *Candida dubliniensis* is a recently identified yeast mostly isolated in HIV-positive individuals with oral Candidiasis. It shares diagnostic characteristics with *Candida albicans* but presents often an increased resistance to anti-fungal drugs (Schorling, Kortinga *and all.*).

HUMAN DISEASES DUE TO CANDIDA

Allergy, cutaneous and mucoral Candidiasis organ related infection and systemic diseases or be associated with endocrine syndromes.

■ **Candida, Urticaria and Atopic Dermatitis:** Urticaria seems to be a common form of *Candida* allergy. In a previous study of our group 119 (25,5%) of 465 patients with positive skin tests to fungi had urticaria. 70% of these patients had positive skin tests to *Candida albicans*.

In a recent survey of Candidiasis we have found that 12 (20%) of 58 patients had urticaria and 4 only chronic itching without wheals and erythema.

IgG antibodies significant by indirect immunofluorescence (greater than 80) titers were found in 41 patients and IgM in 2. Specific IgE *Candida* antibodies was positive in 9 patients (6,4%) in contrast with the better sensitivity of skin tests. Thyroid disease was found in 6 patients (3 hyperthyroidisms 2 hypothyroidisms and

one simultaneous decrease or TSH and control implying a thyroid surrenal compromise. In 8 patients antithyroid antibodies have been found. Antinuclear antibodies were positive in 10 patients (7,1%). These data confirm a mosaic of *Candida* allergy, auto-immune disorders and endocrine compromise in urticaria linked to *Candida*.

■ **Candida and Respiratory Allergy:** *Candida* allergy in asthma and allergic rhinitis has been reported by many authors in the last 40 years (Brunet, Charpin, Dhivert, Girard, Kourilsky, Oliveira *et al.*, Savolainen *and all.* 1998; Sclafer, Sclafer and Hewith, Sclafer and Thibault).

In a previous series 52 (44%) out of 465 patients with positive skin tests to fungi had asthma or allergic rhinitis.

From 58 cases of Candidiasis recently reviewed 24 were atopic as defined by usual criteria for other antigens total and specific IgG for inhalants. Half (12) of these had rhinitis and 6 asthma and rhinitis. From the group of 38 non-atopic patients with recurrent *Candidal* infection also had rhinitis.

Immunotherapy with *Candida* extracts was tried in 70 patients generally after one of two courses of itraconazole or fluconazole. A clinical improvement was observed in the patients treated with vaccines.

CANDIDIASIS

■ **Oral Candidiasis:** Oral Candidiasis is a common form of Candidiasis.

■ **Muco-cutaneous Candidiasis:** Mucocutaneous Candidiasis is a very common form of *Candidal* infection. We will consider first the chronic form which is usually considered as a primary immunodeficiency (IUIS Scientific Committee, Palma-Carlos and Palma-Carlos, Roberts and Stiehm, WHO Scientific Group).

■ **Chronic Mucocutaneous Candidiasis:** Chronic mucocutaneous Candidiasis is a form of persistent Candidiasis usually caused by *Candida albicans* of the skin, nails and mucous membranes that occur in patients with various metabolic disturbances or defect in cell mediated immunity. Chronic mucocutaneous Candidiasis can present a more limited form of chronic oral hyperplastic Candidiasis. (Ellis, Herrod, Kirk-Patrick 1999, Lehner).

■ **Muco-cutaneous candidiasis:** In a group of 58 (57 females, 1 male) cases of mucocutaneous Candidiasis a large spectrum of clinical manifestations have been found. 46 adult females had recurrent complicated vulvovaginitis, 31 patients had thrush, 26 skin lesions,

12 onychomycoses and 3 diarrhea. In the most current forms of disease there is therefore an usual association of multiple Candidal lesions, 12 of these patients presented also chronic urticaria.

■ **Onychomycosis:** In our series of mucocutaneous Candidiasis onychomycosis has been observed in 12 out of 58 patients (20%) all were associated with other lesions.

■ **Vulvovaginal Candidiasis:** Vulvovaginal Candidiasis is common in women. Vulvovaginal Candidiasis may be classified into complicated and uncomplicated forms (Sobel *and all.*).

For uncomplicated forms of Candidial vaginitis the severity is mild to moderate, the frequency sporadic, the infecting organism *Candida albicans*. In contrast in complicated forms the disease is severe, recurrent.

- Two thirds of the patients (66%) had a decrease in cytotoxic cells, more often NK cells CD16CD56, but also in CD8 cytotoxic ;
- In 2 patients (5%) NK and CD8 cells were normal but IgG specific antibodies to *Candida* were absent. Globally a defect in the defense factors implied in antibody cellular cytotoxicity (ADCC) NK or CD8 cells, or *Candida* antibodies has been found in 36 (80%) out of 44 patients studied. These data suggest that a combined cellular and humoral defense mechanism as antibody dependent cellular cytotoxicity (ADCC) play a central role in most cases of complicated Candidial vulvovaginitis.

■ **Urinary Tract Candidiasis:** The most common risk factors for Candidial tract infection include urinary tract instrumentations, recent antibiotic therapy and advanced age. *Candida* is now the most frequently isolated organisms from the urina of patients in surgical intensive care units. (Benett, Ellis, Klepser *and all.* Le Wis and Klepser, Shoham and Levitz).

Local contamination is more common in women. *Candida* cystitis or bladder colonization may be caused by prolonged catheterisation with concomitant antibiotic treatment, diabetes with glycosuria, anatomical uropathy, previous bladder endoscopy or surgery, diabetic neurogenic bladder, chronic outlet obstruction from prestatic hypertrophy or pelvic irradiation for cervical cancer (Benett, Ellis).

Candidial pyelonephritis is more frequently the result of hematogenous dissemination but could also be the results of an ascending infection. The appearance of a fungal conglomerate in the renal pelvis is rare but could be a complicating factor (Ellis). The formation of this fungal ball is conditioned by obstruction of the urinary tract, localized papillary necrosis, urethral or bladder catheters and diabetes. In Candidiasis patients catheter change rarely results in elimination of candi-

duria but discontinuation of the catheter alone may result in eradication of Candidiasis in almost 40% of the patients. (Ellis, Kwon-Chong). Up to 80% of patients with disseminated Candidiasis also have renal infections and associated Candiduria but urine cultures are generally non reliable for the diagnosis of disseminated infection (Ellis). In a patient with Candiduria is difficult to distinguish between colonization, contamination and infection. Is important to distinguish between renal infection and cystic infection alone. The isolation of *Candida* in urine specimens obtained by suprapubic aspiration, positive blood cultures and an increase in serological evaluation of *Candida* antibodies are important factors to consider in these cases (Benett, Ellis, Kwon-Chung and Benett).

■ **Other Forms of Candidiasis:** In immunocompromised patients, drug addicts or HIV positive patients, different atypical forms of Candidiasis can be observed including arthritis, osteomyelitis, skin lesions, ocular lesions, myalgia, cholecystitis, prostatitis, pancreatic abscesses. (Ellis, Kwon-Chung and Benett, Odds). Other forms comprise: Candidial Balanitis, Oesophageal Candidiasis, Gastrointestinal Candidiasis, Hepatic and Hepatosplenic Candidiasis, Candidial Infections of the Gallbladder, pancreas and Peritoneum, Candidial Endocarditis Myocarditis and Pericarditis, Candidial Suppurative Phlebitis, Pulmonary Candidiasis, Osteoarticular Candidiasis, Candidial Meningitis, Candidial Endophthalmitis, Neonatal and Congenital Candidiasis, *Candida* Septicemia and Disseminated Candidiasis.

ASSOCIATION WITH AUTO-IMMUNE ENDOCRINE SYNDROMES

Candidiasis could be associated with autoimmune endocrine syndromes affecting different endocrine glands. The association of chronic mucocutaneous Candidiasis, hyperparathyroidism and Addison's disease is usually found in autoimmune polyendocrine syndrome type I (APS-I) or poly glandular autoimmune (PGA-I) Peterson *and all.*

In our series endocrine disorders have been studied in 18 patients. Parathyroid and surrenal functions were normal in all cases. Hyperthyroidism has been found in 2 cases (11%) and hyperthyroidism in 3 (16%). Antithyroid antibodies have been evaluated in 19 patients. Antibodies to thyroglobulin and peroxidase were increased in 2 patients and only to peroxidase in 1 case. In 2 euthyroid patients imagiology revealed thyroid nodules. Thyroid auto-immunity seems to be the more frequent auto-immune endocrine disease in mucocutaneous Candidiasis.

Precipitating antibodies prepared from protoplasts are more specific as indicator of Candida infection than antigen prepared from whole cells (Cook, Cutler, Peterson).

CANDIDA ANTIBODIES

Latex Agglutination Test

Latex particles sensitized with a homogenate antigen of *Candida albicans* are reacted with patient serum and contrasera (Bryant).

When latex-agglutination test is positive the patient's serum is serially diluted and tested until a final positive dilution is attained. This is reported as the highest dilution that gives a clear positive reaction. An increase in titer or conversion from negative to positive test or fourfold increase in titers is presumptive evidence of invasive infection (Bryant).

Indirect Immunofluorescence

In our series of Candidiasis IgG, IgM and IgE specific antibodies have been studied. Specific IgG has been determined by indirect immunofluorescence in 43 patients and IgE by Unicap RAST in 44 patients. IgG antibodies were negative in 6 (14%) patients at 1/40 in 2 (5%) 1/80 in 9 (%) patients (borderline) 1/160 (%) in 14 patients (%) at 1/320 in 7 at 1/640 in 3. IgM antibodies were negative in 21 (%) patients, positive at 1/40 in 2 and at 80 in 1 pointing out to a recent infection or reinfection. Specific IgE was negative in all the patients with mucocutaneous Candidiasis even when an immediate reaction was observed in skin tests. Specific IgG normal or high titers are found in 81% of the patients with mucocutaneous Candidiasis pointing to an ineffective humoral response to Candida. In 2 out of 6 patients with null titers natural killer and CD8 cells were normal suggesting an ADCC defense mechanism.

CELLULAR IMMUNITY IN CANDIDIASIS

The decrease in NK activity is in this series the most frequent abnormality of cellular immunity. Together with a decrease of CD8% the decrease in cytotoxic cells attains 34 (66%) of the patients studied. In all the patients with NK decrease Candida IgG antibodies were found in normal or increased levels. Aside of these NK cells decrease a second pattern of disturbed antibody dependent cytotoxicity (ADCC) was found in 2 patients with normal values and percentages of NK

and CD8 cells but no Candida antibodies despite recurrent Candida infections. Therefore 2 thirds of the patients with mucocutaneous Candidiasis, and complicated vulvovaginitis have a defect of cellular immunity and in 5% of the patients cellular immunity is normal but antibodies implied in ADCC (antibody dependent cellular cytotoxicity) together with cytotoxic cells are absent. Recent data suggests that delayed type hypersensitivity to Candida with systemic or organ related symptoms could be detected in vitro by the study in flux cytometry of activated CD4 positive T cells with either CD25 or CD6 positive activation markers (Brunet *and all.*).

IMMUNOPATHOGENESIS OF CANDIDIASIS

However, in our mucocutaneous Candidiasis patients a decrease of CD3-CD16+CD56+ or natural killer cells or less often of CD8 cells was the more relevant finding being present in most cases. An absence of specific anti specific bodies is more rare but also observed in other patients.

Specific cell mediated immunity to Candida can also be decreased.

Administration of killed *Candida albicans* to mice result on transient depression of T-lymphocyte dependent mitogen responses (Ashman). Animals given killed Candida or a polysaccharide extract from Candida develops increase susceptibility to infection with bacteria. Cell mediated immunity including NK cells play a dominant role in the control of Candidiasis as shown in clinics in patients with cell mediated immunity defects as a result of HIV infection after corticosteroid use or in patients with primary immunodeficiency state such as DiGeorge syndrome and also chronic mucocutaneous Candidiasis. (Ashman, IUIS Scientific Committee, Lehman, Patterson. Innate immunity is a dominant protective mechanism against Candida (Shoham and Levitz). Phagocyte killing is by oxidative and non-oxidative mechanisms and may be augmented by opsonization and pro-inflammatory cytokines. It is considered that an IgG1 anti-body titration of 320 or greater points to a recent infection a titer of 80 being normal. As usual the presence IgM antibodies corresponds to a recent infection.

THERAPY OF CANDIDIASIS

Infections due to Candida are the most common of fungal infections and one of first causes of infection in hospitalized, patients and intensive care units.

General preventive measures as removal of catheters and prophylaxis of invasive Candidiasis in patients

groups undergoing therapy that produces prolonged neutropenia are recommended.

From 40 years now Amphotericine B has been the most employed anti-fungal agent. The subsequent introduction of azole antifungal and terbinafine has allowed to treat Candidal infections with lesser toxicity.

A few years ago isolation of *Candida* from clinical specimens were generally labelled as contaminant and disregarded and nowadays most physicians mostly organ specialists still think this way. In the last two decades however *Candida* spp. have emerged as a major cause of human disease. In USA the rate of *Candida* infections increased from 75% in smaller hospital to 407% in large university hospital and marked morbidity and mortality have been linked to infections caused by *Candida*. In current practice also and even in out-patients the rate of *Candida* recurrent infections increased about 250% in the last 5 years as seen in our own series. Therefore research in antifungal therapy although one of the fastest growing in infections diseases still need urgently new drugs.

Fluconazol and itroconazol are the most employed antifungal drugs available.

CANDIDA IMMUNOTHERAPY

Candida immunotherapy can be useful in most patients as shown by our results and previous results. *Candida* immunotherapy has been tried on female patients with complicated forms of vulvovaginitis. After the results of Moraes, Loja, our own series confirm the effectiveness of *Candida* immunotherapy in complicated vaginal Candidiasis 80% of good results and even correction of NK abnormalitie in 70% of the patients.

IMMUNOTHERAPY IN MUCOCUTANEOUS CANDIDIASIS

42 mucocutaneous *Candida* patients have been treated with specific immunotherapy with a *Candida* extract (Allergopharma - Reinbeck, Germany). 10 patients have not yet reached the mean time (1-2 years) for evaluation. From the other 32 in 12 (40%) a total remission of symptoms has been achieved; in 17 (51%) a significant improvement was obtained and only in 3 (9%) there was no significant improvement. As long as CD16/CD56 evolutive D16 was nominated in 1 patient and CD56 in all the 4 patients evaluated until now.

CONCLUSIONS

Candidiasis is a fast growing argument in Medicine. We can consider 2 different patterns of ADCC defense mechanisms in Candidiasis:

- NK cells activity or number decrease ;
- Absence of specific IGG anti *Candida* antibodies in presence of normal NK cells.

Candida allergy and hypersensitivity has been considered during many years as an important factor in allergic diseases, mainly in french literature. In the last few years however *Candida* allergy has been considered irrelevant and even *Candida* vacins have been withdrawn from certain European countries.

On series show that *Candida* is implied in most cases of alelrgic disease and can't be considered only as an occasional contaminant in allergy. The most current form of *Candida* allergy is chronic urticaria but some cases of respiratory disease are also present. *Candida* spp is implied in a large growth of human diseases from immunodeficiencies to septicemia anf from allergy or recurrent infections. *Candida* immunotherapy can be employed not only in certain cases of alelrgy but also in mucocutaneous Candidiasis with complicated vulvovaginitis where all current antifungal treatment fail at mean term.

Autoimmunity has been known to be associated with Candidiasis In adults patient with mucocutaneous Candidiasis thyroid involvement is more frequent as shown by our series.

Candida immunotherapy is effective in most cases of disease due to *Candida* but standardized extracts and vacines must be available to assure better diagnosis and immunotherapy.

Candidiasis must be revisited and the new lines of research developed. There is still a large way to achieve optimal results.

A more detailed study of NK receptors and activity markers is worthwhile in Candidiasis.

References

1. American Society of Clinical Immunology (1994). - Recommendations for the use of hematopoietic colony stimulating factors: evidence based, clinical practice guidelines. *J Clin Oncol* 12:2471-2508.
2. Appleton S.-S. (2000). - Candidiasis: Pathogenesis, clinical characteristics and treatment. *J Calif Dent Ass* 28:942-948.
3. Ashman R.-B. (1998). - Candidiasis albicans - pathogenesis, immunity and host defense. *Res Immunol* 149:281-298.
4. Benett J.-E. (2001). - *Candidiasis*. In: Braunwald E., Fauci A.-S., Kasper D.-L., Hauser S.-L., Longo D.-L., Jameson J.-L. (eds.) Harrison's Principles of Internal Medicine New York : McGraw-Hill pp 1176-1178.
5. Brunet J.-L., Peyramond D., Cozon GJN. (2001). - Diagnosis of normal and abnormal. Delayed type hypersensitivity to *Candida albicans* - detection of specific activation. In flow cytometry. *Allergie Immunologie* 33:115-125.
6. Bryant N.-J. (1992). - Laboratory Immunology and Serology, 3rd edition. Philadelphia : WB Saunders Company pp 307-308.

7. Cook N. (1996). - Serodiagnosis of fungal infections. In Stevens CDS. ed. *Clinical Immunology and Serology*. Philadelphia Davis, pp. 299-306.
8. Cutler J.-E. (1998). - The *Candida albicans* phosphomannan complex in *Candida* host interaction. *Res Immunol* 149:299-305.
9. De Sousa M., Cochran R., Macki G.-R., Parrot D., Arala-Chaves M. (1976). - Chronic mucocutaneous candidiasis treated with transfer factor. *Br J Dermatol* 94:79-88.
10. Dhivert H. (1988). - Desensibilisation au *Candida albicans* in J. Bousquet, ed. *Desensibilization Spécifique*. Paris : Masson, pp. 135-140.
11. Edwards J.-E. (1995). - *Candida* species in Mondell G.-L., Bennett E. and Dolin R. eds. *Principles and practice of infectious diseases*. New York : Churchill Livingstone pp. 2289-2295.
12. Ellis D.-H. (1994). - *Clinical mycology*. Underdale Australia: Gillingham Printers. Girard J.-P. and Gumovski P. (1985). Chronic asthma due to *Candida albicans*. *Ann. Allergy* 55:280-285.
13. Groll A., Walsh T.-J. (1998). - Pharmacology of antifungal compounds. *Adv Pharmacol* 44 : 343-500.
14. Groll A.-H., Walsh T.-H. (2001). - Caspofugin: pharmacology, safety and therapeutic potential in superficial invasive fungal infections. *Expert Opin Invest Drug* 10: 1545-1548.
15. Guduri S., Ballas Z.-K. (2002). - Deficient NK-cell function in adult patient with recurrent Non-invasive mucosal candidiasis. *J Allergy Clin Immunol* 109:S186.
16. Hoang A. (2001). - Caspofugin-acetate : an antifungal agent. *Am J. Health Syst. Pharm.* 58:1206-1214.
17. Huang, Johansson SGO., Zargari A. (1995). - Allergen cross reactivity between *Pytyrosporium orbiculare* and *Candida albicans*. *Allergy* 50:648-656.
18. I.U.I.S. Scientific Committee (1999). - Primary Immunodeficiency diseases. *Clin Exp Immunol* 118 suppl 1:1-34.
19. James and Warin R.-P. (1971). - An assessment of the role of *Candida albicans* on food yeasts in chronic urticaria. *Br J Derm* 84:227-237.
20. Keating G.-M., Jarvis B. (2001). - Caspofungin Drugs 61:1121-1129.
21. Kirkpatrick C.-H. (1989). - Chronic mucocutaneous candidiasis. *J Clin Microb Infect Dis* 8:448-451.
22. Kirkpatrick C.-H. (2001). - Chronic mucocutaneous candidiasis. *Pediatr Infect Dis* 20 :17-206.
23. Klepser M.-E., Lewis R.-E., Pfaller M.-A. (1998). - Therapy of *Candida* infections : Susceptibility testing, resistance and therapeutic options. *Ann Pharmacotherapy* 32:1353-1361.
24. Koivikko A., Kalimok, E., Nieminen E., Savolainen J., Viiljanen M., Viander M. (1998). - Allergenic cross reactivity of yeasts. *Allergy* 43:192-200.
25. Kontoyiannis D.-P., Luna M.-A., Samuels B.-I., Bodey G.-P. (2000). - Candidiasis. *Infect Dis Clin North Am* 14:721-739.
26. Kozel T.-H. (1998). - Complement activation by pathogenic fungi. *Res Immunol* 149:281-289.
27. Lehman P.-F. (1993). - *Immunity to fungi*. In : Lachmann P.-J., Peters K., Rosen F.-S., Walport M.-D. and Lehner T. (eds). *Clinical Aspects of Immunology*. Oxford : Blackwell Scientific.
28. Lehner T., Buckley H.-E., Murray G. (1990). - The relationship between fluorescent agglutinating and precipitating antibodies to *Candida albicans* and their immunoglobulin classes. *J Clin Pathol* 25:344-352.
29. Lehner T. (1993). - *Immunological aspects of oral disease*. In: Lachman P.-J., Peters, Rosen F.-S. and Walport M.-J., eds. *Clinical aspects of Immunology*. Blackwell Scientific : Oxford pp 2027-2077.
30. Lewis R.-E., Klepser M.-E. (1999). - The changing face of nosocomial Candidemia: Epidemiology resistance and drug therapy. *Ann J Health Syst Pharm* 56:525-533.
31. Mathews R., Burnie J. (1998). - The role of antibodies in protection against candidiasis. *Res Immunol* 149:343-351.
32. Monteiro F., Loja, Cavalcanti C. (1996). - Investigaç o e tratamento de vulvovaginitis recorrente por C ndida. *Rev Bras Alerg Immunopatologia* 16:99-155-156.
33. Moraes PSA. (1993). - Candidiase vaginal de repeti  o. *Rev Bras Alerg Immunopat* 16:155-156.
34. Moraes PSA., Lima-Goiaba S., Taketomi E.-A. (2000). - *Candida albicans* allergen immunotherapy in recurrent vaginal candidiasis. *J Invest Allerg Clin Immunol* 10:305-309.
35. Moraes PSA., Taketomi E.-A. (2000). - Allergic vulvovaginitis. *Ann Allergy Asthma Immunol* 85 :253-267.
36. Nyirjesy P. (2001). - Chronic vulvovaginal candidiasis. *Am Fam Physician* 15:697-702.
37. Palma-Carlos A.-G., Palma-Carlos M.-L. (1991). - *Incidence of primary and acquired immunodeficiencies in an out-patient population*. In: Chapel H.-M., Levinsky R.-J., and Webster ADB. (eds). *Progress in Immune deficiency III*. London: Royal Society of Medicine pp. 98-100.
38. Palma-Carlos A.-G., Palma-Carlos (2001). - Chronic mucocutaneous candidiasis revisited. *Allergie Immunologie* 33:229-232.
39. Palma-Carlos A.-G., Palma-Carlos M.-L. (2004). - *Candidiasis*. In *Mycology Handbook of Fungal Biotechnology* 493-503. Arora D. K. ed. Marcel Dekker in New York, Basel.
40. Rex J.-H., Walsh T.-J., Sobel J.-D., Filler S.-G., Pappas P.-G., Dismukes W.-E., Edward J.-E. (2000). - Practice guidelines for the treatment of candidiasis. *Clin Infect Dis* 30:662-678.
41. Rivas V., Rogers T.-J. (1983). - Studies on the cellular nature of *Candida albicans* induced suppression. *J. Immunol*. 130:376-38.
42. Rigg D., Miller M., Metzger J. (1990). - Recurrent vaginal candidiasis : Treatment with *Candida* allergen immunotherapy. *Am J Obs Gynecol* 162:331-336.
43. Rosedale N., Brown K. (1979). - Hyposensitization in management of recurring vaginal candidiasis. *Ann. Allergy* 43:250-253.
44. Savolainen J., Kortekans, Savolainen O., Nermes M. (1998). - IgE, IgA and IgG responses to common yeasts in atopic patients. *Allergy* 53:506-512.
45. Savolainen J., Lamminta K., Kalino K., Viander M (1993). *Candida albicans* and atopic dermatitis. *Clin Exp Allergy* 23 :332-339.
46. Sayag J. (1992). - *Allergie fungique*. In: Charpin J. and Vervloet D. eds. Paris : Flammarion, M dicine-Sciences, pp. 03-816.
47. Sclafer J., Thibault M. (1986). - *Allergie Mycosique*. In: Charpin J. (ed) *Allergologie*. Paris, Flammarion p. 721-730.
48. Schorling S.-R., Kortinga H.-C., Froscyb M., Muhlschegel F.-A. (2000). - The role of *Candida dubliniensis* in oral candidiasis. *Gut Rev Microbiol* 26:59-68.
49. Segura T., Ballas Z.-K. (1998). - Natural Killer (NK) cell defficiency in a patient with chronic mucocutaneous candidiasis. *J Allerg. Clin Immunol* 105 : suppl, S 74.
50. Shoham S., Levitz S.-M. (2000). - *Immune response to fungi*. In: Rich R., Fleischer T.-A., Shearer W.-T., Kotzin B.-L., Schroeder H.-W.. eds. *Clinical Immunology* London : Mosby, pp 311-317.
51. Singh N. (2001). - Changing spectrum of invasive candidiasis and its therapeutic implications. *Clin Microbiol Infect* 7, supp 2, 1-7.
52. Sobel J.-D., Far O.-S., Force R.-W. (1998). - Vulvovaginal candidiasis: epidemiological, diagnostic and therapeutic considerations. *Am J Obst Gynec* 178:23-11.
53. Sobel J.-D. (2000). - Practide guidelines for the treatment of fungal infections. *Clin Infect Dis* 30 :62-661.
54. Song Y.-H., Li Y., MacLaren N.-K. (1998). - *Adrenal autoimmunity and the auto- immune polyglandular syndrome type I-III*. In: Rose N, and Mackay T. *Autoimmune diseases*. San Diego, Academic Press, pp 725-736.
55. Yarrow D., Meyer S.-A. (1998). - Proposal for the amendment of the diagnosis of the Genus *Candida*. *Int J Syst Bacteriol* 2:611-615.
56. Wey S.-B., Mori M., Pfaller M.-A., Woolson R.-F., Wenzel R.-P. (1998). - Hospital acquired Candidemia. The attributable mortality and excess lenght of stay. *Arch Intern Med* 148:2642-2645.