A Review on Oral Candida as Commensal and Opportunistic Pathogen

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Abstracts

Oral candidiasis, commonly referred to as "thrush," is an opportunistic fungal infection that commonly affects the oral mucosa. The various forms of oral and maxillofacial candidiasis are pseudomembranous, acute, chronic, median rhomboid glossitis, perioral dermatitis, and angular cheilitis. The main causative agent Candida albicans, is a highly versatile commensal organism that is well adapted to its human host, continuing rise in the development of pathogenicity and resistance to traditional antifungal agents. Thus needto develop novel therapeutic strategies that can find the early resistance to particularantifungal. So the clinician can be better able to prescribe effective antifungal for oral candidiasis.

Keywords: *Oral candidiasis; Candida albicans; anti fungal treatment.*

Introduction

The species of Candida is present inside the oral cavity together as an opportunistic and commensals pathogens. In the current years, incidence noteworthy in the state of pathogenic of commensal been seen and reflected by increased escalation of infrequent and common candidiasis forms.[1] The morbidity in oralcandidiasis may as discomfort, chronicpain, limiting mastication especially in immune-deficient and in elderly patients. There exist clinical multiple presentations of oesophageal and oropharyngeal Candidiasis created by candidaalbicans both alone/in infection of mixed type. The treatment is based upon the Candidiasis type-(pseudomembranous, acute, chronic, angular cheilitis etc.) and severity of infection. Hence the review presently comprehends opportunistic pathogen oral Candida.[2] The Candidaalbicans exists primarily as a fungus of dimorphic form. The ability of Candidaalbicans is transforming into various forms morphologically like hyphae, yeast & psuedohyphae by the signals from the environmental perception which is significant for virulence.[3,4] The psuedohyphae are referred to ellipsoidal, elongated cells which are adherent to each other, while the true type of hyphae cells characterized with a morphology of cellular cylindrical and the walls of septal are perpendicularly separated.[5] Infection of fungal type is the thrush or Candidiasis which is attributable to any species of Candida genera among which is Candidaalbicans, the causative common species.[6,7]

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Scientific classification of Candida species:

Kingdom: Fungi, Phylum: Ascomycota, Subphylum: Saccharomycotina, Class: Saccharomycetes, Order: Saccharomycetales, Family: Saccharomycetaceae, Genus: Candida

Formation of Germ tube -The germ tube arises from the Candidaalbicans as lateral short filamentous form growth cells.[8,9] It's mentioned that tube of germ, grows as Candida being cultured on medium of solid example Sabouraud Dextrose Agar (SDA) & depending on formation of germtube leads to the character for identification of *Candidaalbicans*.[10,11] According to Davis 1972 germ tube of C. albicansis opportunistic, which increases its virulence. And it is the most important factor in virulence by giving mechanical power to resist the phagocytic cells of the host.[12,13]

Antifungal therapy: According to Nguyen 1996 incidence for fungal severe infections is due to opportunisticfungi which raised in about previous years particularly those with mycoses of endemic and the patients who are immunocompromised with the main problem of the public related to health in many countries of the world can give rise to seriousside effects on the host. The points majorly attacking are the cell wall which is rigid and the metabolism of their sterol with peculiarities by this all of the fungi is distinguished from the cells for potentialhosts.[14-16]

Although fewer studies were done comparing directly to azoles, related to treatment for endemic mycoses,the oral azoles have availability which ensures tolerated better treatments for the Candidaalbicans. This is useful particularly for diseases of fungal which need longlive courses therapeutically, like coccidimycosis/ for mycoses of endemic occurring in AIDS.[16,17] Tortora 1995 reported that many drugs that inhibit or kill fungi are therefore quite toxic for humans. Besides, most fungi have a detoxification system that modifies many antibiotics, probably by hydroxylation, as a result; the added antibiotics are fungistatic only as long as repeated application maintains high levels of unmodified antibiotic.[18] There are reports for fungal increased infections along with that resistance to several antifungal, leading to the demand to develop and discover effective new drugs for antifungal.[19-21] The chitin enzyme synthase target of active fungal antibiotics- polyoxin D along with Nikkomycin.[22] Therapy of antifungal was categorized into tropical and systemic agents.[23] According to Uzun 2014 the patients with immunocompromised diseases or patient's having underlying severe diseases, the prognosis is poor of these patients and this generally comes under fungal systemic infection.[24]. But a rapid and reliable method for determination antifungal susceptibility that would hence needful in patients management along with the fungal invasive diseases.[25]

The primary antifungal agents for oral candidiasis:

Azoles: Azole medications are a family of antifungal drugs which are use full and important drugs of antifungal ending with"-azole" as suffix. The azole exists in class for members of five heterocyclic nitrogen ring compounds comprising of one atleast another atom of noncarbon for sulfur, nitrogen, or oxygen.[26] The important two diazoles comprising of fluconazole and itraconazole.[27,28]

Fluconazole: It an antifungal drug, used to treat fungi. And it's drug of antifungal used for treating fungi along with bistriazole fluorinated that's unusual as being soluble in water at pH neutral solubility which permits administration orally or intravenously.[27,29] Fungal systemic infections also are effectively often treated with Fluconazole. The Fluconazole effective for oral Candidiasis andcandidiasis of the oesophageal in the patient's suffering from AIDS, along with that its also useful among the patients who are immunocompromised[25,30,31] and patients suffering from AIDS along with blastomycosis and cryptococcosis,[27] it also has an activity which is good for dermatophytes.[32,33]

Side effects: Fluconazole in lactating mothers is not recommended since in the human milk the fluconazole secreted at about concerntrations same to that of plasma. The Fluconazole's has rarely also been related with lethal or severe hepatotoxicity. Along with this it's used cautionly in the patients already suffering with disease of the liver, preexisting in human beings. But few people allergic towards azole, therefore who all allergic for azole of other kind drugs maybe allergic for flucanazole. Few drugs of azole have side effects that they disrupts the production of estrogen during pregnancy.[34]

Drug susceptibility and drug Resistance: Susceptibility of *C.albicans* and non albican Species of Candida-Itraconazole, Amphotericin B, Fluconazole, Echinocandin, Candidaalbicans, Flucytosineand Candidatropicalis is susceptible to above antifungals

usually. While *Candidaglabrata, Candidakrusei, Candidadubliniensis* shows various ranges from Susceptible; Susceptible dose-dependent; Susceptible-intermediate to Resistant. The species of Candida causes infections that is treated by various drugs of antifungal available, but resistance of drug poses problem seriously to patient's individual health and nowadays the health system management been difficult. Several studies have shown that several factors responsible for drug resistance includes the pumping of drugs out from the cells of fungal type, the targets are modified by the incorporating point mutations in the genes the modification of main enzymes by pathways of biosynthetic and the modulation for factors of transcription plays.[35]

Historical perspective: The fungi occur as eukaryotic, free living organisms, those exist like moulds- filamentous fungi, yeasts-round fungi/ combination of the two- dimorphicfungi. According to Terezhalmy 2011 Candidiasis found orally is the commonest infection of fungal type, affecting mucosa of the oral cavity. And the lesions caused from yeast (Candidaalbicans).Candidaalbicans one components for oral normal micro-flora along with (30%-50%) of people. The rate increases by patient's age. These Candidaalbicans recovered by 60% patient's with dental problems in the mouths above 60 yrs of age. According to Prasanna 2012 the species of Candida are of different types–seen inside oralcavity.[36, 37] Mostly the oral species of Candida consists of: *Candidaglabrata, Candidakrusei, Candidapsuedotropicalis, Candidaguillermondii, Candidatropicalis, Candidaparapsilosis, Candidaalbicans, Candidastellatoidea*.[38]

Biology of *Candida albicans:* Candida albicansis true and most common opportunistic fungal pathogens. It is termed as "commensal" organism because it can found in the normal flora of skin, oral cavity, gastrointestinal tract, vaginal and the urinary environments. According to Ellis1994 and Ferreira 2010 it is found in the all environment, on leaves, flowers, water, and soil.[39,40] The *Candidaalbicans*–a yeast fungus,grampositive, thin walled, morphology which is microscopic showing spherical – oval about diameter of 5 um. It's larger to bacteria, that is reproduced by the process of budding as Yeast.[41,42] *Candidaalbicans* grows in moderate temperature's at a temperature ranging from (20-38) degrees centigrade and can resist pH to ranges (2.5-7.5).[43] According to Ellis,1994 the agar of dextrose Sabouraud containing gentamycin or chloramphenicol flavored to isolate Candida.[39] *Candida albicans* can grow better oncormeal, 72hours following with incubation of 25°C forming branched abundantly pseudo hyphae along with the blastoconidia and truehyphae are represented. These blastoconidia formed are clusters of grape like along the length of hyphae. If incubation period is extended a terminal chlamydoconidia may be formed.[44] *Candida albicans* have more than one wellknown and important features that it has ability of fermenting the sugars along with fermenting other kind of carbohydrates to produce ethanol.[45] The *Candidaalbicans* are fungus (dimorphic) which gives rise to two types of forms—Invasive & noninvasive. The form of yeast is the noninvasive and form of hyphal by which it can penetrate mucosa; is invasive. Under different environmental conditions the *Candidaalbicans* shows variant which are morphologically different forms: the forms that include are—yeast budding cells (blastoconidia, truehyphae, blastospores, clamydospores and pseudo hyphae along with this which are used in identifying *Candidaalbicans* among the different types of species for Candida. The C. albicans produces these germtubes and transition to hyphal form. However, ability in assuming different forms that is related towards pathogenicity for organism.[46,47]

Life as a successful commensal: The *Candidaalbicans* which is largely fungus of asexual type; but by physiologically and morphologically is variable highly along with that the fungus's adaptability and is of pleomorphic type which is capable of growing like budding yeast/as pseudo mycelium for conjoined and elongated cells of yeast or truehyphae which consists of generated parallelsided with growing-tip filaments.[48] And also exhibits nonsexual variation form called switching of phenotype that is able to generate cells which are stable and variant colony with properties i.e. distinctive.[49] According to Vautier 2015 *C. albicans* that adapted of commensalism & which thrive in various host of niches (mucosa of the oral cavity, vagina, skin, gut).[50] Hence state of host immune response & along with this mediated specific organism adaptations is responsible for the change in host related state of commensal.[51] According to Yamaguchi 2005 Changes to the availability for nutrients inside gut by intake through diet, further can impact in abundance for Candida[52] & due to diet change/fungal gut microbiota leads to dysbiosis & pathologies of inflammation origin like Crohn'sdisease.[53,54] Hence commensal for Candidiasis status is also related with micro biome host as whole & immunestatus for host.

Life as a successful opportunistic pathogen: Throughout the infection pathway the colonized *Candidaalbicans* different hostniches, comprising of differences as eg. Changes in pH, carbon dioxide levels, hypoxia, availability of nutrient in the medium.[55,56] According to Sokol 2016 that the one important features of Candidaalbicans like that of a pathogen which is successful adaptability in various other conditions.[55] It has been seen that the microenvironment of the host have sources of carbon that is heterogeneous therefore the adaptation of candidaalbicans for using simultaneously the sources of carbon alternatively for the virulence and survival.[57,58] The metabolic characteristic and Candida's flexibility also leads alterations in cellular secretome and proteome[59] and the ability of undergoing yeast into hyphaltransition, opaque, white with switching[60] formation of biofilm also the characteristic of adhesive property,[59,61] and capacity of remodeling.[56-52] The changes within composition of cellwall's polysaccharide changes the pathogens susceptibility to stress from environment & antifungals.[55-61] apart from the environment effect's immunogenically along with altering presentation and expression of critical pathogen associated molecular patterns(PAMPs) so the *Candidaalbican's* makes a target to move for the recognition along with immunesystem of the host.[56-63] As per Crawford 2015, humanhost retains micronutrients (Zn, Mn, Fe,Cu) from pathogen by the process called as nutritionalimmunity.[64] Within the pathogen such micronutrients essential towards various cellular vital functions.[64] These adaptive evolutionary traits makes Candidaalbicans survival possible in different hostniches; countering the host immunity defence's and makes the *Candidaalbicans* itself to establish as pathogen which is successful. Mandell 1994 reported that Candida is a fungus and was first isolated in 1844 from the sputum of a tuberculosis patient.[65] Andseveral studies have demonstrated that infection with candida is associated with certain pathogenic variables. Pathogenicity of candida depends on local and systemic factors of host.

Akpan 2002 reported that the gland of salivary functions which is impaired is susceptible to candidiasis in the oral cavity. Whereas proteins of antimicrobial saliva like sialoperoxidase, lactoferrin, histidine rich in polypeptides, lysozyme and antibodies for anticandidal that is specific, interacts to the mucosa of the oral cavity and inhibit the overgrowth for Candida.[66] According to Epstein 1990 and Guida 1988 by which there is adherence for Candida with acrylic is enhanced when the flow of saliva under fittings of denture surfaces is reduced, denture fittings improper and with the poor oral hygiene.[67,68] Dreizen 1984 reported that the wearing dentures increases theinfection with candida is as many as 65% of elderly people. Since wearing of synthetic products produces a microenvironment conducive to the growth of candida with low oxygen, low pH, and an anaerobic environment.[69] According to Brassart 1991 Candida adhesing onto the epithelial surface, is an important step, this promoted with definite components of fungal like C3dreceptors, mannose, saccharins, and mannoprotein.[70-72]

Different Drugs such as inhaled steroids have been shown to increase the risk of oral candidiasis.[72] by possibly suppressing cellular immunity and phagocytosis and drugs such as broad spectrum antibiotics alter the local oral flora creating a suitable environment for candida to proliferate. According to Garber 1994 the mucosal local immunity changes towards normal by discontinuating the steriod's inhaled.[73] Ohman 1988 reported that the Candida growth within the saliva is enhanced with glucose being present & adherence with epithelial cells in the oral cavity.[74] According to Guida 1988 those who are having low immunity they mostly prone to Candia disease.[68] Thus the various factors be diabetes, smoking, immunosuppressive state like malignancies (leukaemia, infection HIV etc) and deficiency of nutrition intake have been implicated particularly to change of commensal candida to pathogenic candida that leads to onset of candidiasis.

Conclusion

In recent period fungal infection is risen up enormously. Most of the people of many countries are suffering from Candidiasis. Sometime different antifungal agents failing to treat the fungal diseases completely. Due to this ineffectiveness of drugs they became side effects to the human. This appearance of resistance to antifungal drugs, which demands to discover and development of new effective antifungal drugs for this we have to search gene which could be responsible to develop drug resistance in Candidiasis, more often for *Candida albicans*. Also with molecular tools, we can know the effective antifungal at the earliest. These novel strategies will overcome the oral candidiasis problems in the near future.

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References

1. Williams D, Lewis M. Pathogenesis and treatment of oral candidosis. J. Oral Microbiol. 2011;3: 5771. doi:10.3402/jom.v3i0.5771
2. Sherman RG, Prusinski L, Ravenel MC, Joralmon RA. Oral candidosis. Quintessence Int. 2002;33: 521–532.
3. Kourkoumpetis T, Manolakaki D, Velmahos G,et al. Candida infection and colonization among non-trauma emergency surgery patients. Virulence 2010; 1(5): 359-66.
4. Van der Meer, JW, van de Veerdonk, FL,et al. Severe Candida spp. infections: new insights into natural immunity. Int. J. Antimicrob. Agents 2010;36(2): 58-62.
5. Mohamed SP, Muzzammil S, Pramod KT. Buccoadhesive dosage form containing antifungal agent for treating oropharyngeal candidiasis: A review. Current Drug Therapy, 2011;6: 55-64
6. Antifungal chemotherapy in patients with acquired immuno deficiency syndrome. British Society for Antimicrobial Chemotherapy Working Party. Lancet, 1992:340(8820): 648-51.
7. Li, FQ, Ma CFet al Diagnostic value of immunoglobulin G antibodies against Candida enolase and fructose-bisphosphate aldolase for candidemia. BMC Infect. Dis.2013;13: 253.
8. Papon N, Courdavault V, Clastre M, Bennett RJ. Emerging and Emerged Pathogenic Candida Species: Beyond the Candida albicans Paradigm. PLoSPathog. 2013; 9(9): e1003550. doi:10.1371/ journal.ppat.100355.
9. Phan GT, Belangen PH, Filler SG. Roleof hyphal formation in Interactions of Candida albicanswith endothelial cells. Infect. Immun. 2000; 68 (6): 3485 – 3490.
10. Odds FC. Candida and candidiasis. Leicester. Leicester Univ. press. 1979. (A) Odds FC. Candida and Candidosis. Baltimore. University Park Press.1979; 104110.
11. Sobel JD. Muller G. Buckley HR. Critical role of germ tube formation in the pathogenesis of Candidalvaginitis. Infect. Immun. 1984; 44(3):576-580.
12. Davis RR, Denning, TJV. Candida albicansand the fungicidal activity of the blood. Sabouraudia. 1972; 10:301-312.
13. Calderone RA, Braun PC. Adherence and receptor relationship of Candida albicans. Microbilogy Reviews. 1991; 55:1-20.
14. Nguyen MH, Peacock JE, Morris AJ, Tanner DC, Nguyen ML, Syndman DR, Wagener MM, Rinaldi MG, Yu VL. The changing face of candidemia emergence of non–Candida albicans species and antifungal resistance Am. J. Med. 1996; 100:617 – 623.
15. Salvo D. Microbiology and Immunology. chapter3. Mycology, the University of South Carolina, USA.2009.
16. Lortholary O, Denning DW, Dupont B. Endemic mycoses. a treatment update J. Antimicrob. Chemother. 1999; 43(3):321 – 331.
17. Pujol I, Fernandez – Ballart J, Gurro J. Iffect of inoculum from on in vitro antifungal susceptibility of Aspergillus spp. J. Antimicrob. Chrmother. 2001; 47:715 – 718.
18. Tortora GJ, Funke BR, Case C. L. Microbiology an introduction. Antimicrobial drugs.1995; 49 – 514.
19. Ernst EJ, Klepser ME, Pfaller MA. Postantifungaleffectsofechinocadin, azole and polyene antifungal agents against Candida albicansand Cryptococcus neoformans. Agents Chemother. 2000; 44 (4):1108-11.
20. Zhong W, Jeffriea MW, Georgopapdakou NH. Inhibition of inositol phosphoryceramide synthesis by aureobasidin An in Candida and Aspergillus species Antimicrob. Agents Chemother. 2000; 44(3):651-653.
21. Espinal– Ingroff A, Bartlett M, Chaturvedi V, Ghannoum M, Hazen KC, Pfaller MA, Rinaldi M, Walsh TJ. Optimal susceptibility testing conditions for detection of azole resistance in Aspergillus spp. NCCLS collaborative evaluation. antimicrob. Agents Chemother. 2001; 45:1828–1835.
22. Smith EB. Topical antifungal drugs in the treatment of tinea pedis, tinea cruris and tinea corporis, J Am. Acad. Dermatol. 1993;28(5):24-28.
23. Fitzpatrick JE. Fitzpatricks dermatology in general medicine (5thed.) Freedberg IM, Elsen AZ, Wolf K. Vol 2 Chapt. 1999; 247, p: 2737.
24. Uzun O, Ascioglu S. Anaissie EJ. Rex JH. Risk factors and predictors of outcome in patients with

cancer and breakthrough candidemia. Clin. Infect. Dis. 2001; 32:1713 – 1717.

25. Chen J, Wan Z, Li R. Modified colorimetric assay for susceptibility testing of azole antifungal drugs against Candida species. Journal of clinical microbiology. 2004 Apr 1;42(4):1790-3.
26. Eicher T, Hauptmann S. The Chemistry of Heterocycles. Structure, Reactions, Synthesis, and Applications (2nd ed.) John Wiley & Sons. 2003.
27. Kwon-Chung KJ, Bennett JE. Candidiasis (moniliasis, thrush, Candida paronychia, Candida endocarditis, bronchomycosis, mycotic vulvovaginitis, candiosis) In. Cann C, editor. Medical mycology. Philadelphia, Pa. Lea & Febiger. pp. 1992; 280–336.
28. Johnson LB, Kauffman CA, Veroconazole. A new tiazole antifungal agent. Clin. Infect. Dis. 2003;36:630 – 637
29. Tortora GJ, Funke BR, Case CL. Microbiology an introduction. Antimicrobial drugs. 1995; 49 – 514.
30. Colombo AL, Barchiesi F, McGough DA. Rinaldi MG. Comparision of E test and National committee for Clinical Laboratory Standards broth macrodilution method for azole antifungal susceptibility testing J. ClinMicrobiol. 1995;33:535-40.
31. MA, Montero O, Quindo s, G. A comparative evaluation of E test and broth microdilution method for fluconazole and itraconazole susceptibility testing of Candida spp. J. Antimicrob. Chemother. 1999;43:477- 481.
32. Jessup CJ, Warner J, Isham N, Hassan I. Ghannoum MA. Antifungal susceptibility testing of dermatophytes. establishing a medium for inducing conidial growth and evaluation of susceptibility of clinical isolates J. Clin. Microbiol. 2000;38:341 – 344.
33. Ghannoum MA, Chaturvedi V, Epsinel – Ingroff A, Pfaller MA, Rinaldi MG, Lee – Yang, W. and Warnoch, D.W.. Intra and inter laboratory study of a method for testing antifungal susceptibilities of dermatophytes. J. Clin. Microbiol. 2004;42:2977 – 9.
34. Kragie LT, Stephanie DP, Christopher JC, Charles LS, David M. "Assessing Pregnancy Risks of Azole Antifungals Using a High Throughput Aromatase Inhibition Assay". Endocrine Research 2002;28(3):129–40.
35. Pappas,P.G.,Kauffman,C.A.,Andes,D.,Benjamin,D.K.Jr.,Calandra,T.F.,Edwards,J.E.Jr.,et al. Clinical practice guidelines for the management of candidiasis:2009 update by the Infectious Diseases Society of America. Clin. Infect. Dis. 2009;48: 503–535.doi:10.1086/596757.
36. Terezhalmy GT, Huber MA. Oropharyngeal candidiasis. Etiology, epidemiology, clinical manifestations, diagnosis, and treatment. Crest Oral-B at dentalcare.com ContinEduc Course. 2011;1–16.
37. Prasanna KR. Oral candidiasis – A review. Scholarly J Med. 2012;2:6–30.
38. Dangi YS, Soni MS, Namdeo KP. Oral candidiasis. A review. Int J Pharm Pharm Sci. 2010; 2:36–41. 4. Ellis, D.H. Clinical Mycology. The human opportunistic mycosis. Gillingham printers PTY Ltd. Australia. 1994.
39. Ellis DH. Clinical Mycology. The human opportunistic mycosis. Gillingham printers PTY Ltd. Australia.1994
40. Ferreira C, Silva S, Faria-Oliveira F, Pinho E, Henriques M, Lucas C. Candida albicansvirulence and drug-resistance requires the O-acyltransferase Gup1p. BMC Microbiology. 2010;10:238-251.
41. Webb BC, Thomas CJ, Willcox MDP, Harty DWS, Knox KW. Candida associated denture stomatitis aetiology and Management. Areview. Part I factors in fluencing distribution of Candida species in oral cavity. Austrian Dental J. 1998;43(1):45-50.
42. Kayser FH, Bienz KA, Eckert J, Zinkernagel RM. Medical Microbiology. Thieme Stuttgart, New York. PP. 2005;229-233, 348-374.
43. Rinaldi MG. Biology and pathogenicity of Candida species. In: Bodey GP. Candidiasis. Diagnosis and Tretment, 2P nd P ed. Raven Press, New York. 1993
44. Sutton DA, Fothergill AW, Rinaldi MG. Guide to Clinically Significant Fungi, 1st ed. Williams & Wilkins, Baltimore. 1998
45. Bhavan PS, Rajkumar R, Radhakrishnan S, Seenivasan C, Kannan S. Culture and identification of Candida Albicansfrom vaginal ulcer and separation of enolase on SDS-PAGE. Inter. J. Bio. 2010;2 (1):84-93.
46. Molero G, Díez-Orejas R, Navarro-García F, Monteoliva L, Pla J, Gil C, Sánchez-Pérez M, Nombela C. Candida albicans. genetics, dimorphism

and pathogenicity. Internatl. Microbiol. 1998;1:95–106.

47. Salvo D. Microbiology and Immunology. chapter3. Mycology, The University of South Carolina, USA. 2009
48. Soll DR. The role of phenotypic switching in the basic biology and pathogenesis of Candida albicans. J Oral Microbiol 2014;6:22993.
49. Netea MG, Joosten LAB, van der Meer JWM, Kullberg B-J, van de Veerdonk FL. Immune defence against Candida fungal infections. Nat Rev Immunol 2015;15:630-642.
50. Vautier S, Drummond RA, Chen K, Murray GI, Kadosh D, Brown AJP, Gow NAR, MacCallum DM, Kolls JK, Brown GD. Candida albicans colonization and dissemination from the murine gastrointestinal tract: the influence of morphology and Th17 immunity. Cell Microbiol 2015;17:445-450.
51. Neville BA, d'Enfert C, Bougnoux M-E. Candida albicans commensalism in the gastrointestinal tract. FEMS Yeast Res 2015;15.
52. Yamaguchi N, Sonoyama K, Kikuchi H, Nagura T, Aritsuka T, Kawabata J: Gastric colonization of Candida albicans differs in mice fed commercial and purified diets. J Nutr 2005; 135:109-115.
53. Sokol H, Leducq V, Aschard H, Pham H-P, Jegou S, Landman C, Cohen D, Liguori G, Bourrier A, Nion-Larmurier I et al. Fungal microbiota dysbiosis in IBD. Gut 2016 http://dx.doi.org/10.1136/gutjnl-2015-310746.
54. Li Q, Wang C, Tang C, He Q, Li N, Li J. Dysbiosis of gut fungal microbiota is associated with mucosal inflammation in Crohn's disease. J ClinGastroenterol 2014;48:513-523.
55. Brown AJP, Budge S, Kaloriti D, Tillmann A, Jacobsen MD, Yin Z, Ene IV, Bohovych I, Sandai D, Kastora S et al. Stress adaptation in a pathogenic fungus. J ExpBiol 2014; 217:144-155.
56. Hall RA. Dressed to impress. impact of environmental adaptation on the Candida albicans cell wall. MolMicrobiol 2015;97:7-17.
57. Brown AJP, Brown GD, Netea MG, Gow NAR. Metabolism impacts upon Candida immunogenicity and pathogenicity at multiple levels. Trends Microbiol 2014; 22:614-622.
58. Childers DS, Raziunaite I, MolAvelar G, Mackie J, Budge S, Stead D, Gow NAR, Lenardon MD, Ballou ER, MacCallum DM et al. The rewiring of ubiquitination targets in a pathogenic yeast promotes metabolic flexibility, host colonization and virulence. PLoSPathog 2016; 12:e1005566.
59. Ene IV, Heilmann CJ, Sorgo AG, Walker LA, de Koster CG, Munro CA, Klis FM, Brown AJP. Carbon source-induced reprogramming of the cell wall proteome and secretome modulates the adherence and drug resistance of the fungal pathogen Candida albicans. Proteomics 2012;12:3164-3179.
60. Lan C-Y, Newport G, Murillo LA, Jones T, Scherer S, Davis RW, Agabian N: Metabolic specialization associated with phenotypic switching in Candida albicans. Proc Natl AcadSci U S A 2002, 99:14907-14912.
61. Ene IV, Adya AK, Wehmeier S, Brand AC, MacCallum DM, Gow NAR, Brown AJP. Host carbon sources modulate cell wall architecture, drug resistance and virulence in a fungal pathogen. Cell Microbiol 2012;14:1319-1335.
62. Lewis LE, Bain JM, Lowes C, Gillespie C, Rudkin FM, Gow NAR, Erwig L-P. Stage specific assessment of Candida albicans phagocytosis by macrophages identifies cell wall composition and morphogenesis as key determinants. PLoSPathog 2012; 8:e1002578. 116 Parasitic and fungal diseases Current Opinion in Microbiology 2016;34:111–118
63. Hall RA, Gow NAR. Mannosylation in Candida albicans: role in cell wall function and immune recognition. MolMicrobiol 2013;90:1147-1161.
64. Crawford A, Wilson D. Essential metals at the host–pathogen interface. nutritional immunity and micronutrient assimilation by human fungal pathogens. FEMS Yeast Res 2015;15.
65. Mandell GL, Bennett JE, Dolin R. Principles and practice of infectious diseases. 4th ed. New York. Churchill Livingstone; 1994; Anti-fungal agents; pp. 401–10.
66. Akpan A, Morgan R. Oral candidiasis. Postgrad Med J. 2002;78:455–9.
67. Epstein JB. Antifungal therapy in oropharyngeal mycotic infections. Oral Surg Oral Med Oral Pathol1 990;69:32–41.
68. Guida RA. Candidiasis of the oropharynx and oesophagus. Ear Nose Throat J1988;67:832–40.
69. Dreizen S. Oral candidiasis. Am J Med1984;30:28–33.

70. Brassart D, Woltz A, Golliard M, et al. In-vitro inhibition of adhesion of Candida albicans clinical isolates to human buccal epithelial cells by Fucα1→2Galβ-bearing complex carbohydrates. Infect Immun 1991;59:1605.
71. Douglas LJ. Surface composition and adhesion of Candida albicans. Bio Soc Trans 1985;13:982.
72. Milne LJ, Crompton GK. Beclomethasone dipropionate and oropharyngeal candidiasis. BMJ1974; iii:797–8.
73. Garber GE. Treatment of oral candida mucositis infections. Drugs 1994;47:734–40.
74. Ohman SC, Jontell M. Treatment of angular cheilitis: the significance of microbial analysis, antimicrobial treatment, and interfering factors. Acta Odontol Scand 1988;46:267–72.