Factors influencing adherence of *Candida* spp. to host tissues and plastic surfaces

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Attachment of *Candida* spp. to host tissues and plastic surfaces is the first and a crucial step that initiates colonization by yeast cells and subsequent development of disseminated fungal infection. These infections are associated with high degree of morbidity, mortality and extra cost. Modern trends have focused not only on how best to treat but also on how to prevent Candida infections. To achieve this goal, the factors that influence the adherence of *Candida* spp. to biological and non biological surfaces have been studied. *C. albicans* adheres at a degree higher than that of the other *Candida* spp. and *C. tropicalis* adheres to a lesser extent. This may reflect the higher pathogenicity of *C. albicans* compared to the other *Candida* spp. Germinated *C. albicans* cells adhere to host tissue more readily than do yeast-phase. Sugars play an important role in the adherence of *Candida* spp. Overall, galactose was found to promote the adherence of *Candida* spp. to host tissues and plastic surfaces more than any other mono or disaccharide. Amino sugars on the other hand inhibit the adherence of the yeast cells. Divalent ions such as Ca$^{2+}$ and Mg$^{2+}$ promote the adherence of *Candida* spp. more than monovalent ions. *Candida* spp. express on their surface receptors, which interact with a wide variety of host proteins including fibrinogen, fibronectin, laminin, and type I and IV collagen thus binding *Candida* spp. To glycoproteinaceous conditioning film at the blood-polymer interface. Coaggregation of *Candida* spp. with other bacteria promotes colonization of yeast cells to oral biofilm, host tissues, and to surfaces of the indwelling vascular catheters. These factors form the basis for the interference with the adherence of *Candida* spp.

Despite major advances in treatment and diagnostic techniques in the past decade, critically ill patients in the general hospital population and in medical and surgical intensive care units have become prime targets for opportunistic fungal infections. These infections are associated with high degree of morbidity; mortality and extra cost and mainly attributed to *Candida* spp. Candida infection is not restricted to immunocompromised patients but healthy individuals are also liable to these infections. A study conducted by the National Nosocomial Infections Surveillance (NNIS) described the change in the frequency of primary blood stream infections between 1980 to 1990 in ICUs in 124 hospitals in the United States. According to this study, the incidence of primary blood stream fungal infections due to Candida increased by 487% in large teaching hospitals, by 219% in small teaching hospitals, and by 370% in large non-teaching hospitals. The increase in Candida infections was even greater than that of *Staphylococcus aureus*, enterococci, and aerobic-negative bacilli. A more recent study conducted by NNIS showed that the highest number of nosocomial fungal infections occurred in the following categories: burn/trauma, cardiac surgery, oncology, high-risk nursery, and general surgery. Central intravascular catherization is one of the major causes for the increasing incidence of fungemia.

Adherence is the first and a crucial step that leads to colonization and subsequent infection by microorganisms. There is little doubt that survival of microorganisms in various niches is dependent on their ability to adhere to surfaces or substrates. In general, there is a positive correlation between the adhesion and infectivity of the microorganism. There are several evidences that support this view. One of the most convincing and probably the most widely accepted is that bacterial adhesion endows the pathogen with the ability to withstand cleansing mechanisms (such as secretions, ciliary action, salivation, swallowing excretion, cough etc.) operating on mucosal and endothelial surfaces. It is believed that there is a close relationship between adherence capability and infection potential of Candida e.g. *C. albicans* adheres to vaginal and buccal epithelial cells to a significantly greater degree than other less virulent species.
Modern trends have focused not only on how best to treat but also on how to prevent Candida infections to avoid the associated morbidity, mortality and extra cost. One way to achieve this goal is to interfere with adherence. Use of various medical devices including indwelling vascular catheters, cardiac pacemakers, prosthetic heart valves, chronic ambulatory peritoneal dialysis catheters and prosthetic joints has greatly facilitated the management of serious medical and surgical illness. However, successful development of synthetic materials and introduction of these artificial devices into various body systems has been accompanied by the ability of microorganisms to adhere and colonize these devices, which leads to the formation of the biofilm. The biofilm acts as source of infection and protects microorganism from the activity of the antimicrobial agents and from host defense mechanisms. As a result, implant associated infections are difficult to resolve and the implants must be removed. Central venous catheters (CVCs) are associated with the highest rate of sepsis. It has been estimated that 3 million CVCs are inserted annually in the United States. This associated with at least 120,000 cases of CVCs associated septicemia. Therefore, it is not surprising that vascular catheters are a major source of nosocomial sepsis and contribute to the majority of nosocomial cases of septicemia due to Staphylococcus epidermidis, Staphylococcus aureus, and C. albicans.

A study conducted by Beck-Sague and Jarvis at facilities conducting hospital-wide surveillance showed that Candida spp. accounted for 78% of all nosocomial fungal infections and C. albicans accounted for 76% of all candida infection. Adherence of C. albicans to mucosal cells, fibrin-platelet matrices, and vascular endothelial cells has been examined to elucidate early events in the pathogenesis of mucosal colonization and infection, candidal endocarditis and tissue invasion from the intravascular space. Mucosal cells from different locations in the host have been extensively used to study the adherence of C. albicans. These include corneocytes, buccal epithelial cells, vaginal epithelial cells, gastrointestinal mucosal cells, and HeLa cells, a human cervical epitheloid carcinoma cell line. Metastatic infection after hematogenous dissemination of Candida species is presumably dependent on the fungus traversing the vascular endothelium. While C. albicans and C. tropicalis were capable of directly traversing the endothelial surface, viridans group streptococci, although adherent, were incapable of vascular penetration. Adherence and penetration of Candida to lymph node tissue was confined to subcapsular spaces and trabecular sinuses. In the spleen, yeast cells bind to the marginal zones and in the kidney to convoluted tubules, glomeruli, and tunica media of arterioles.

C. tropicalis is the second most frequent isolate and with C. albicans they are the most frequently isolated yeasts from the human oral cavity. C. tropicalis adheres to the epithelial cells and to fibrin clots as much as C. albicans. Other yeasts including Torulopsis glabrata, C. parapsilosis, C. pseudotropicalis, C. guilliermondii, C. stellatoidea, and S. cerevisiae adhere to a lesser extent than C. albicans.

Several assay techniques are now available to quantify the adherence of the yeast cells to host tissues and to plastic surfaces. Microscope can simply be used to count the attached yeast cells to tissues or to visualize yeast adhering to acrylic surfaces while the test material remains immersed in buffer. Other assay techniques include: using radiolabelled cells, tetrazolium salt, XTT, fluorescence assay based on using fluorescent dye Calcofluor white, which binds to chitin and glucan in the yeasts, and by immunofluorescence assay.

The mere potential of adherence of the microorganisms to a particular substratum is not sufficient to initiate colonization of the substratum because factors such as nutritional requirements and resistance to deleterious physical and chemical pressures are also important. Elucidation of mechanisms of adherence and factors influencing this process are the keys by which interference with this early event can be achieved. This discussion is not aimed to review the adherence mechanisms of Candida spp. or discuss the applied models to study this process. We discuss the different factors that influence the adherence of Candida spp. to host tissues and to non biological surfaces.

(A) Environmental factors

1) Sugars

Sugars play an important role in the adherence of Candida spp. to the host tissues and to plastic surfaces. There are two general approaches in studying the effects of sugar on the adherence of yeast. By pre-growing the organisms on the tested sugar or by adding the sugar to the test medium in which adher-
ence is measured. Some sugars promote adherence of yeast because they are required as the main ingredients of the extracellular materials that facilitate the attachment of the organism. Some others inhibit adherence by competing with the yeast for the binding sites.

Carbon sources are involved in the production of extracellular polymeric materials (EP) that are produced by certain Candida spp. This material originates from the cell surface of Candida and it is believed to be responsible for yeast adhesion. The chemical composition of this material showed that it is mannoprotein in nature containing carbohydrate (85-90%) and protein (7-9%) (mannose was the major sugar making about 82-87% of the total carbohydrates), glucosamine (1.5%) and phosphorus (0.5%). McCourtie and Douglas reported that EP isolated from culture supernatants of C. albicans grown on carbon sources (50 mM glucose, 500 mM sucrose or 500 mM galactose) was of similar composition. However, galactose-grown yeasts, which are the most adherent, produced more EP than sucrose-grown organisms and glucose-grown yeasts (the least adherent) gave the lowest yield of EP. Lectin-like proteins (adhesin) with affinities for L-fucose, N-acetyl-D-glucosamine and D-mannose containing glycoproteins of epithelial cells were detected in EP isolated from five strains of C. albicans. They found that adhesion of C. albicans GDH 2346 to buccal and epithelial cells was inhibited primarily by L-fucose whereas adhesion of strain GDH 2023 was inhibited by N-acetyl-D-glucosamine, or D-glucosamine. Reinhart et al. found that the attachment of C. albicans to the vaginal epithelial cells increased by dextrone, galactose, mannose, alpha-methyl-mannoside, N-acetylglucosamine, N-acetyl-galactosamine, and N-acetylmannosamine and decreased by amino sugars glucosamine, galactosamine, and mannosamine. He suggested that adherence of Candida may not require specific yeast adhesin-cell receptor interaction. Crithley and Douglas demonstrated the importance of protein portion of the mannoprotein over carbohydrate moiety for adherence. They found that the EP isolated from culture supernatants of C. albicans inhibited yeast adhesion to buccal epithelial cells by 60%. They also found that pre-treatment of EP with sodium periodate or alpha-mannosidase had little or no effect while pretreatment with dithiothreitol or proteolytic enzymes either partially or completely destroyed its ability to inhibit adhesion.

Kaita isolated adhesive substances (AS) from the surface of C. albicans IFO 1385 grown in different carbon sources. These substances are responsible for the adherence of C. albicans to acrylic and contained 62-68% carbohydrate (as glucose) and 23-26% protein. He found that cells that cultured on YNB medium containing 500 mM galactose showed a much greater tendency to adhere than those cultured in the YNB containing 500 mM glucose.

The effects of sugars on the adherence of Candida spp. to biological and non biological surfaces depend on the type of sugar and the sugar concentration. Overall, galactose potentiates the adherence of yeasts more than do glucose and other sugars. The increase in adherence in galactose-grown yeasts over those grown in other sugars may be attributed to the increase in the EP production, increase in the rate of spheroplast formation or increase in the cell hydrophobicity. Macura and Tondya studied the effects of incubation of C. albicans with different sugars on the adherence to epithelial cells. They found that D-glucose, D-galactose and sucrose significantly enhanced the adherence, and so did D-mannose, while incubation with D-xyllose, D-ribose, D-fructose, maltose, lactose and raffinose did not. El-Azizi et al. showed (Fig. 1) that adherence of C. albicans CA51 to polystyrene was promoted in presence of galactose and other tested sugars more than in the presence of glucose. Amino sugars and mannose are known to inhibit the adherence of yeasts. Amino sugars are involved in the formation of EP and other adhesin

![Fig. 1 - Adherence of C. albicans CA51 to polystyrene in YNB medium with 500 mM of different carbon sources.](image-url)
such as chitin\textsuperscript{52}. Adherence of \textit{C. albicans} to epithelial cells\textsuperscript{16,53} and to polystyrene\textsuperscript{51} (Fig. 2) was inhibited by amino sugars. Mannose significantly decreased the attachment of \textit{C. albicans} to epithelial cell\textsuperscript{54}. Pre or post treatment of duodenal discs with mannose, N-acetylglucosamine prevents the adherence of \textit{C. albicans} to GIT. The saccharide may bind to the GIT mucosa and block the attachment of \textit{C. albicans}\textsuperscript{55}.

McCourtie and Douglas\textsuperscript{44} reported that adherence of \textit{C. albicans} to acrylic surface was proportional to the concentration of sugars on which the organism were pre-grown. El-Azizi \textit{et al.}\textsuperscript{51} showed (Fig. 3) that maximum adherence of \textit{C. albicans} to polystyrene was obtained when the organism was incubated with 50 mM of glucose and at higher concentrations the adherence was inhibited.

2) Metal ions

Adherence of \textit{Candida} spp. to host tissues and to the plastic surfaces is affected by the presence of metallic ions. Divalent ions such as Ca\textsuperscript{2+} and Mg\textsuperscript{2+} promote adherence by reducing the forces of electrostatic repulsion that exist between the organism and its negatively charged substratum\textsuperscript{55}. With enteric bacteria, Zn\textsuperscript{2+}, Fe\textsuperscript{3+} and Fe\textsuperscript{2+} promote adherence to buccal epithelial cells more than with either Ca\textsuperscript{2+} or Mg\textsuperscript{2+}\textsuperscript{56}. Adherence of \textit{C. albicans} to acrylic was increased by addition of Ca\textsuperscript{2+} and to less extent by Mg\textsuperscript{2+} and Mn\textsuperscript{2+} and slightly inhibited by monovalent cations\textsuperscript{44}. El-Azizi \textit{et al.}\textsuperscript{51}, showed that the adherence of \textit{C. albicans} CA51 to polystyrene was promoted by the addition of divalent cations especially Mg\textsuperscript{2+} and was inhibited by Fe\textsuperscript{2+} (Fig. 4). Increase of calcium concentration was accompanied by further increase in adherence of \textit{C. albicans}\textsuperscript{44}.

Adherence of \textit{C. albicans} to the extracellular matrix proteins type I collagen and fibronectin is dependent on the presence of extracellular calcium. Calcium-dependent fungal cell wall glycoproteins, likely related to integrins may be receptors responsible for yeast cell adherence to host tissue\textsuperscript{57}. Calcium, and to a lesser extent, cesium and magnesium, enhanced yeast adherence to host tissue\textsuperscript{57} and divalent cation chelators reduced it\textsuperscript{39,57}. Phosphate-buffered saline (PBS) had no effect on the adherence of \textit{C. albicans} to buccal epithelial cells\textsuperscript{58}.

3) pH

pH is an important environmental factor which should be considered in the adherence of yeast to host tissues. Adhesion of \textit{C. albicans} to epithelial cells was optimum at pH 6 to 7 in either PBS or tissue culture medium\textsuperscript{14,58,59}. Samaranyake and MacFarland\textsuperscript{60} showed that adhesion of \textit{C. albicans} in citrate and phosphate buffers was slightly enhanced at pH 7 and more highly enhanced at pH 3 with Hela cells as the substrate.

The vaginal lumen is normally an acidic environment with a pH between 5 and 6\textsuperscript{61,62}. Since the vaginal mucosa is constantly exposed to an environment containing CO\textsubscript{2}\textsuperscript{62}, it is possible that this gas could be important during adhesion and pathogenesis. This is illustrated in clinical studies which suggest that in diabetes and during pregnancy there is an increased tendency to retain CO\textsubscript{2}\textsuperscript{63-65} as well as an increased

![Fig. 2](image-url) Adherence of \textit{C. albicans} CAS1 to polystyrene in YNB medium with 50 mM of different amino sugars.

![Fig. 3](image-url) Adherence of \textit{C. albicans} CAS1 to polystyrene in YNB medium with different concentrations of glucose.
predisposition for candidiasis. One of the results of an increase of CO₂ is a decrease in pH. Persi et al. found that adherence of *C. albicans* to vaginal epithelial cells was increased at low pH.

Mehentee and Hay found that adherence of two strains of *C. albicans* to stomach mucosal cells fluctuated as the pH was raised from 1.2 to 3.4 and optimal adherence by both strains to jejunal mucosal surfaces occurred at neutral pH.

4) Temperature

The adherence of yeast is affected by incubation temperature. Candida can grow over a wide range of temperature and because adherence precedes growth, it is not surprising to find that adherence also occurs at wide temperature range. The extent of *C. albicans* binding to cultured human keratinocytes was dependent on the incubation temperature. Incubation temperature affects hydrophobicity and germination of yeast cells, and these play important roles in the adherence of yeast. *C. albicans* cells grown at room temperature were more hydrophobic than cells grown at 37°C (ref. 34). A strong correlation was shown between germination and increased adherence of *C. albicans* to human buccal epithelial cells. Conditions permitting germination enhance adherence of *C. albicans*. Germination of *C. albicans* in saliva occurs at 37°C and not at 25°C (ref. 72). Merkel and Phelps found that specific interactions between the yeast cells and fibroblasts only occurred at 37°C and Kimura and Pearsall reported that adherence of *C. albicans* to buccal epithelial cells in presence of saliva was greater at 37°C than at 25°C.

Kaita found that a large number of the adherent cells of *C. albicans* to acrylic was obtained when the acrylic plates were incubated at 37°C. El-Azizi et al. showed that the adherence of *C. albicans* CA51 to polystyrene at 37°C was higher than that observed at 20, and 25°C however adherence was maximum at 40°C (Fig. 5).

(B) Host proteins

Interaction between host proteins, from fluid and/or matrix phases containing fibronectin, fibrinogen, collagen and laminin, and the infecting organisms forms the basis of adherence and subsequent infection. After contact with blood, a polymer surface such as an intravenous catheter is almost immediately coated with a glycoproteinaceous conditioning film at the blood-polymer interface. This film acts as a binding site for a variety of microorganisms. Recent investigations have revealed that *C. albicans* expresses on its surface receptors, which interact with a wide variety of host proteins including fibrinogen, fibronectin, laminin, and type I and IV collagen. The adherence of *C. albicans* to extracellular matrix (ECM) proteins is dependent upon the presence of extracellular calcium. Hemoglobin induces both promiscuous and specific receptors for ECM proteins and therefore may regulate matrix ad-
hesion during dissemination of C. albicans infection. Because these proteins possess heparin-binding domains, glycosaminoglycans (GAGS) including heparin, heparin sulfate and dextran sulfate inhibit the adherence of C. albicans to subendothelial ECM and ECM proteins by masking a preferred ligand for candida.

1) Fibrinogen
Fibrinogen binds a variety of bacteria such as Staphylococcus aureus, group A streptococci, Streptococcus agalactiae and Escherichia coli. C. albicans has been shown to bind to human fibrinogen in infected tissues. Fibrinogen binds more strongly to hyphae than to germ tubes. Bouali et al. reported that fragments D and E (terminal degradation products of fibrinogen) showed affinity to C. albicans but fragment D possessed a higher affinity than fragment E. Binding of fibrinogen was diminished when C. albicans was pretreated with 2-mercaptoethanol alone or in combination with pronase, or pretreated with alpha-mannosidase or trypsin.

2) Fibronectin
Fibronectin is a peripheral glycoprotein that is widely distributed on the surfaces of normal cells. The structure of fibronectin is characterized by the presence of several distinct domains with binding sites for specific ligands such as heparin sulphate, collagen, and hyaluronic acid. Fibronectin also contains an RGD (Arg-Gly-Asp) sequence recognized by members of class of integral membrane glycoproteins called integrins. By virtue of structure, and the outermost location of fibronectin on the cell surface, this glycoprotein is eminently suitable to mediate contacts between cells and their environment. Many different bacteria are able to bind to membrane-associated fibronectin. In 1978, Kuusela showed that S. aureus could bind to fibronectin. Fibronectin serves as a receptor that binds the organisms to various cell types as well as biomaterials that become coated with it on insertion into host tissues. Skerl et al. described the role of fibronectin in the adherence of C. albicans to buccal and vaginal epithelial cells. C. albicans possesses at least one type of cell surface receptor for binding soluble fibronectin. This receptor apparently is used to bind the fungus to immobilized ECM proteins and to subendothelial ECM. Klotz et al. showed that fibronectin and a peptide, containing the sequence arginine-glycine-aspartic acid (RGD), inhibited candida adherence to subendothelial extracellular matrix protein by more than 90%. Yeast cell adherence to type I and IV collagen, fibronectin and laminin was blocked by peptide fragments from de-natured type I collagen (gelatin). The fragments presumably inhibit adherence by blocking receptors (adhesins) on the surface of the fungus.

3) Laminin
Laminin is a large glycoprotein found mainly in basal membrane and to a lesser extent in plasma. Laminin receptors have been found on cells that normally interact with basement membranes as well as cells that extravasate such as metastatic tumor cells, granulocytes, lymphocytes and macrophage. Laminin has the ability to bind bacteria such as S. aureus and E. coli. C. albicans has been shown to bind to laminin. Klotz studied the adherence of C. albicans to ECM proteins. He found that laminin showed an increase of adherence of 300% above control value. Glycosaminoglycans (GAGS) inhibit the binding of C. albicans to ECM proteins including laminin. Ollert et al. reported that CDPGYIGSR-NH2, which is a synthetic adhesive peptide derived from the laminin B chain, had more inhibitory activity than the RGD peptides in reduction of C. albicans adherence to cultured human keratinocytes.

4) Collagen
Most cells are coated with a layer of glycoproteins that are bound to the cell surface by noncovalent bonds with either a peripheral or integral constituent. It may take the form of matrix, as in mature cartilage where it is composed of a collagen proteoglycan-hyaluronic acid complex that is associated with the cell membrane via fibronectin. Several studies reported the role of collagen type I (ref. 27, 57, 75, 88), type III (ref. 70) and type VI in the adherence of yeast to host tissues. Klotz showed that binding of C. albicans to ECM proteins was inhibited when the proteins were preincubated with specific antibody, except with type IV collagen. A dose-dependent reduction in C. albicans binding to cultured human keratinocytes was observed with collagen type III (ref. 70). Negre et al. showed that 30 kDa proteolytic fragment from the gelatin/collagen-binding domain of fibronectin is a potent inhibitor of fibronectin binding to C. albicans.

(C) Factors related to the adherent cells
1) Morphology and growth phases
The adherence capability of yeast cells varies among the different species and even within the same
Overall *C. albicans* adhere at a degree higher than that of the other *Candida* spp. The in vitro adherence of *C. albicans* and *C. tropicalis* to endothelium was greater than the other *Candida* spp.57. While Samaranayake et al.32 reported that the in vitro adherence of *C. albicans* and *C. tropicalis* to clot was higher than that of the other *Candida* spp., Maisch and Calderone6 showed that highest adherence was observed with *C. albicans* and *C. stellatoidea*. El-Azizi et al.41 found that *C. albicans* CA51 adhere to polystyrene at a higher degree compared to the other *Candida* spp. Hawser33, reported that adherence of *C. krusei* to plastic was greater than that of *C. albicans*.

Inoculum size is an important factor that affects the adherence of yeast. In vitro adherence of *C. albicans* to plastic surface41 (Fig. 6) and to host tissues such as endothelial cells39 or clot53 were directly proportional to the concentration of yeast cells. Kaita35 showed that Cells of *C. albicans* prepared by standing cultivation adhered to acrylic than did those prepared by stirring cultivation. Significant differences in adhesion to buccal epithelial cells29,75 and to polystyrene41 were also noted when *C. albicans* was grown in different media (Fig. 7).

Cell morphology and growth phases are factors that should be considered in studying the adherence of yeast. Klotz et al.94 studied the role of cell size and shape on adherence of *Candida* spp. to plastic. They found that different strains of the same species or even different *Candida* spp. that have close shape and size identically adhered to styrene. The yeast-mycelium transition is an important phenomenon in the acquisition of adhesive property5. Stationary-phase yeast cells adhered better than log-phase cells55.
Fig. 8—SEM showing coaggregation of *Staphylococcus epidermidis* with *C. albicans* on vascular catheter segment (8500X)

Fig. 9—SEM showing coaggregation of *Pseudomonas aeruginosa* with *C. albicans* on vascular catheter segment (6000X)
Holmes et al., reported that adherence of C. albicans was greatest when the yeast had been grown to mid-exponential growth phase. A strong correlation was shown between germination and increased adherence of C. albicans to epithelial cells, indicating that germination or other changes in the fungi accompanying germination were responsible for enhanced adherence. There are several studies that support this finding. Kimura and Pearsall found that partial inhibition of germination by cysteine resulted in comparably lower adherence. San Millan et al. found that after germination of C. albicans had occurred, the fungi could be killed with formalin without interfering with their rapid and efficient adherence to epithelial cells.

2) Surface property
Bacteria adhere to the complementary substrata by ionic or coulombic interactions, by hydrogen bonding, by hydrophobic effect, and by coordination complexes involving multivalent metal ions. Candida spp. adhere to plastic surfaces by what have been called hydrophobic forces, but are more properly designated as attractive London van der Wall forces. Recent studies have revealed that hydrophobic cells of the opportunistic pathogenic fungus C. albicans are more virulent than hydrophilic cells. From a different standpoint, the closer the surface free energy of the substrate surface and the yeast cell, the higher is the probability of adherence. Samaranayake et al. found a positive correlation between the cell surface hydrophobicity (CSH) and adhesion of C. krusei to HeLa surfaces but not to acrylic surfaces. Hazen reported that adherence of C. albicans to epithelial tissues is mediated primarily by specific adhesion receptor interactions that is dependent on CSH. The effect of CSH on adherence of yeast is inter and intraspecies dependent. Relative hydrophobicity of C. albicans and T. glabrata was found to vary with the growth phase, growth medium, and temperature.

All living cells (including yeast) possess a net negative surface charge. According to the DLVO theory, microorganism and most biological substrata can not adhere because both are negatively charged and repulse each other. The theory states that repulsion is a result of electrical double layer existing on any substratum suspended in an electrolyte. The electrostatic layer surrounding the microorganisms is composed of negatively charged surface macromolecules and positively charged counterions. There is an electrical potential across the double layer. The electrical potential is a function of electrophoretic mobility and net surface charge (zeta potential) of the cell. The nature of the electrolytes surrounding the microorganism also affects the electrical potential of surface double layer. For example, divalent ions reduce the electrostatic potential more than monovalent ions and so potentate the adherence of the microorganism to the substrate. Klotz showed that some yeast cells possess electrostatic charge and some other do not. Klotz et al. studied the role of electrostatic charges in the adherence of yeasts to hydrophobic surfaces by altering the surface charges via neutralization of the carboxyl and amino groups.

3) Interaction with other microorganisms
The interaction between yeast cells and other microorganisms (mainly bacteria) may take the form of coaggregation or competition for adherence site. Several studies showed the coaggregation between yeast and other bacteria that include different Streptococcus species, E. coli, Klebsiella pneumoniae, and Porphyromonas gingivalis. C. albicans coaggregates with a variety of streptococcal spp., an interaction that may promote oral colonization by yeast cells. Holmes et al. reported that in the oral biofilm, C. albicans and C. tropicalis bind to S. gordonii NCTC 7869 while C. krusei and C. kefyr do not. They identified a complex cell wall polysaccharide of S. gordonii as the coaggregation receptor for C. albicans. S. epidermidis (Fig. 8) and Pseudomonas aeruginosa (Fig. 9) coaggregate with C. albicans in the biofilm formed on the vascular catheter. That would mean that the biofilms of C. albicans could offer a site for colonization by other fungi or bacteria.

There are some factors that control the coaggregation of yeast cells with bacteria. For example, starvation of yeast cells for glucose increased their coaggregating activity with streptococci by at least tenfold. The concentration of bacteria that coaggregate with yeast should also be considered. Nair and Samaranayake studied the effect of four different species of oral bacteria S. salivarius, S. sanguis, E. coli and Porphyromonas gingivalis on the adhesion of C. albicans and C. krusei to denture acrylic surfaces. They found that exposure to high bacterial concentration resulted in a consistent reduction in candidal adhesion, except for E. coli. Centeno showed that E. coli 07KL (piliated bacteria) enhanced C. albicans at-
attachment to epithelial cells more than *Klebsiella pneumoniae* (non-piliated bacteria). On the other hands, Jenkinson *et al.* found that there was no correlation of cell surface hydrophobicity, of either yeast or streptococcal cells, with their abilities to coaggregate.

Branting *et al.* reported that firm adhesion of *C. albicans* to acrylic occurred when the yeast was incubated simultaneously with *S. mutans* and coaggregation occur in sucrose although adherence of *C. albicans* was less in the same medium alone. Competition with yeast cells for the substrate is another form of interaction with other microorganisms. Kennedy and Volz studied the colonization of *C. albicans* to gastrointestinal mucosa of Syrian hamsters. He found that the indigenous intestinal microflora reduced the mucosal association of *C. albicans* by forming a dense layer of bacteria in the mucus gel, outcompeting yeast cells for adhesion sites, and producing inhibitor substances (possibly volatile fatty acids, secondary bile acids, or both) that reduced *C. albicans* adhesion. Competition was also observed in yeast-yeast interaction. EL-Azizi *et al.* found that adherence of *C. albicans* to polystyrene was reduced when *C. tropicalis* was added with or before the addition of *C. albicans*.

The understanding of the factors that influence the colonization of tissues and prosthethic devices by *Candida* spp. (particularly *C. albicans*) is essential to the development of strategies to reduce or prevent such colonization and subsequent infections. Modification of the environmental and biological factors that promote adherence need to be studied in detail and the factors that reduce the adherence can be used as prophylactic and or therapeutic agents. These strategies are important not only for prevention and treatment of candida infections in general, but also to increase the longevity of prosthetic devices and to decrease the morbidity and expense associated with prosthetic devices related infections.

**References**
