

Adherence of *Candida albicans* to Urinary Catheters

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ABSTRACT

The occurrence of *Candida albicans* in patients with urinary tract infections, and *in vitro* of *C. albicans* to a urinary catheter were studied. *C. albicans* was more adherent to latex rubber than to silicon, whereas *C. tropicalis* adherence was the reverse. The relationship between the adherence and the change in interfacial free energy which corresponds to the process of adherence, suggests that hydrophobic interactions are involved in candidal adherence to catheter materials. Among five *N*-acyl-phenylalanines, *N*-octyl-phenylalanine showed outstanding ability in removing adherent fungi on catheter surfaces.

The use of urinary catheters often brings about urinary tract infections^{4,7,9,31,32}. This has been confirmed by experiments using an animal model³. Several routes by which microorganisms are introduced into the bladder have been suggested¹³, and it may be that adherence of microorganisms plays an important role in the establishment of urinary tract infections. Microbial adherence is the first and essential step in infections, not just those of the urinary tract²¹. Adherence of microorganisms to urinary catheter was studied by several investigators. Sugarman reported *in vitro* adherence of *Escherichia coli* and *Klebsiella pneumoniae* to catheters³³. *Candida* species are often recovered from urine of patients and their contribution to urinary tract infection has been considered^{5,23}. However, few have investigated candidal adherence to urinary catheters. *Candida* species are a normal part of human flora, especially in the oral and vaginal regions, and can be opportunistic pathogens in immunocompromised host or patients undergoing chemotherapy against bacteria. Candidal adherence to

epithelial cells has been investigated by Kimura et al¹², Lee et al¹⁴, Sobel et al³⁰ and Samaranayake et al²⁶. Sundin et al reported that adherence of *C. albicans* to human buccal cells is mediated by mannose residues²⁷. Adherence to acrylic surfaces has been studied by Minagi et al^{17,19}, and they demonstrated that hydrophobic interactions play an important role in this adherence. McCourtie et al¹⁵ and Samaranayake et al^{24,25} suggested that candidal adherence to acrylic surfaces is mediated by polysaccharides. The participation of hydrophobic interactions in adherence to intravenous catheter has been reported by Ashkenazi et al¹ and Rotrosen et al²².

In the present study, we report the adherence of *Candida albicans*, which is the most common *Candida* species, to a urinary catheter.

MATERIALS AND METHODS

Clinical examinations

The occurrence of *Candida* species in patients was investigated during 1985 in the urology ward of Hiroshima University Hospital. The use

of antibacterial drugs was individually based on clinical and laboratory findings. Antifungal drugs were not used in any patient. As a general rule, urinary tract catheters were used in a closed collecting system of CS-Bag® (C.R. Bard Co, NJ, USA), with or without continuous irrigation by polymixin-neomycin solution. In the patients with long-term catheterization, the catheters were changed at two weeks intervals. Urine samples were taken once on admission or before catheterization, three times per week during indwelling catheterization, and once every week after removal of the catheter, and cultured on Uricult® media (Orion Diagnostica, Helsinki, Finland). Bacteria and fungi were grown and identified by standard methods in the Department of Bacteriology of the Hiroshima University Hospital. Bacterial and fungal growth of over 10^4 colony forming units per milliliter was considered as significant. Urinary catheter from patients with candiduria were examined by scanning electron microscopy.

Scanning electron microscopy

A piece of a urinary catheter removed from a patient was fixed in 5% glutaraldehyde in phosphate buffered saline and dehydrated in alcohol. The specimen was placed on a stub using silver DAG, and then coated with gold up to 500 Å thick. The specimen was viewed in a scanning electron microscopy (JSM, T-200, JEOL), and photographed.

Microorganisms

Fungi used in the present study were *Candida albicans* IFO 1385 and *C. tropicalis* IFO 1400. They were maintained on Sabouraud glucose (1% peptone, 0.5% yeast extract, 2% glucose) slants.

Catheter materials

Silicon (Bardex®, all silicon Foley catheter, C.R. Bard Co.) and latex rubber (Bardco®, C.R. Bard Co.) catheter materials were used. These materials, made into sheets (silicon; silicon sheet, Create Medic, Co., Ltd. Yokohama, Japan, latex rubber; Unitika Co., Kyoto, Japan) were also used.

Chemicals

N-acyl-phenylalanines (C₄-C₁₂) (Wu, W. 1985. Investigation of Promoters of 3-Lactam Antibiotics Taken up by the Rectum. Thesis) were kindly provided by Dr. Yata, Institute of Pharmaceutical Science, Hiroshima University School of medicine.

In vitro adherence to catheter material sheets

Catheter materials were made into small sheets (10 × 10 mm, 0.1 mm thick) and washed in distilled water and saline. Precultures of *C. albicans* and *C. tropicalis* were inoculated into fresh media, and incubated at 37°C to the mid log phase of growth. Fungal cells were harvested by centrifugation, washed and resuspended in 0.01 M phosphate saline (PBS, pH 7.0) at concentrations of 1.0×10^7 /ml for *C. albicans* and 1.0×10^5 /ml for *C. tropicalis*. Five small sheets were placed in a plastic petri dish (15 × 90 mm, Corning Glass Works, Corning, NY, USA), to which 50 ml of the fungal suspension were added. The petri dish was incubated at 37°C for 1 hr. The sheets were washed, dried, fixed and Gram stained. Adherent fungal cells in ten high power fields per sheet were counted. Mean adherent cell number and the standard deviation of five sheets were calculated.

Pretreatment of catheter material sheets

To pretreat catheter material sheets, they were immersed in human urine from a healthy donor and incubated at 37°C for 1 hr.

Effect of long-term soaking of catheter materials in aqueous medium

Catheter materials were soaked in PBS at 37°C. Adherence of *C. albicans*, and the contact angles on the surface of catheter materials before and after soaking, were measured.

Removal of adherent fungi

Catheter material sheets to which *C. albicans* had adhered were incubated in the following solutions: 0.1% chlorhexidine, 20 mM ethylenediaminetetraacetic acid (EDTA), 1.0% Triton X-100, 10 mM benzoic acid, 10 mM phenylalanine, 10 mM *N*-acyl-phenylalanine (C₄-C₁₂), and PBS as a control. Then the sheets were washed, dried, fixed, and stained, and adherent fungi were counted.

Contact angle measurement and thermodynamical analysis

The Young contact angles (θ) of distilled water on catheter materials and fungal cells were measured by a drop-on method using a contact angle meter (type CA-A, Kyowa, Tokyo, Japan). Contact angles were measured at ten points on the catheter materials and fungal cell layers, and the mean value was calculated. To measure contact angles on fungal cells, the method of Minagi et al was employed^{17,18}. Briefly, washed fungal

cells were layered on a Millipore filter (pore size 0.45 μm , Millipore Corp., Bedford, MA, USA), dried in air; the contact angles were then measured on this fungal layer.

The change in interfacial free energy which corresponds to the process of adherence (ΔG_a) was calculated from equation (1)⁸⁾.

$$\Delta G_a = \gamma^{\text{SF}} - \gamma^{\text{SV}} - \gamma^{\text{FV}} \quad (1)$$

where

γ^{SF} ; interfacial free energy between the solid and fungal cells

γ^{SV} ; free energy of the solid surface

γ^{FV} ; free energy of fungal cell surfaces

The surface free energy of the solid (γ^{SV}) is given by equation (2), and some derivatives described by Neumann et al²⁰⁾.

$$\cos \theta = \frac{(0.015 \gamma^{\text{SV}} - 2.00)(\gamma^{\text{SV}} \gamma^{\text{LV}})^{1/2} + \gamma^{\text{LV}}}{\gamma^{\text{LV}} [0.015 (\gamma^{\text{SV}} \gamma^{\text{LV}})^{1/2} - 1]} \quad (2)$$

where θ is the Young contact angle of distilled water on the solid, and γ^{LV} is the surface tension of distilled water.

The surface free energy of fungal cell surfaces is given by replacing γ^{SV} with γ^{FV} , and θ on the solid with θ on the fungal cell layer in equation (2).

RESULTS

Cultures positive for *Candida* species were found in six of 1973's (0.3%) total out-patients, and in 14 of 220 (6.4%) in-patients in the urological ward of Hiroshima University Hospital in 1985. Four of six out-patients with positive fungal culture had a history of catheter administration within the preceding year. In one patient, urinary *C. albicans* infection had continued right through in-patient + out-patient status in 1985. Nineteen patients with positive fungal cultures were detected in the urological ward in 1985, and sixteen of them (84.2%) had hospital-acquired candiduria, ten of which (52.6%) were significant. Those ten patients, are presented in Table 1, with the factors with predisposed them to candiduria, plus the clinical features of their infections. Three of these patients (30%) showed a mixed bacterial infection. All of them had urological and/or other diseases which were considered as local and/or systemic factors predisposing them to candiduria. As a systemic factor, antibacterial drugs were being administered in nine out of the ten patients. As

a local factor, indwelling urinary catheters had been installed for various lengths of time in eight of the ten. Their symptoms were mainly pyuria and fever, even if bacteriuria was not detected. Some patients had suffered candiduria for a long period, although usually it disappears without any specific therapy.

Fig. 1 shows the surface of a catheter removed from a patient with a urinary tract infection. Fungal cells in both yeast and filamentous form were observed on the surface of the catheter by scanning electron microscopy.

The *in vitro* adherence assay was performed using catheter material sheets (Fig. 2). *C. albicans* was more adherent to latex rubber than to silicon. In contrast, *C. tropicalis* adhered to silicon in greater numbers than to latex rubber.

To analyze the candidal adherence to catheter materials thermodynamically, surface free energies were calculated from contact angles of distilled water on their surfaces. The contact angles and surface free energies are shown in Table 2. Latex rubber demonstrated higher surface free energy than silicon, as did *C. albicans* compared to *C. tropicalis*.

The change in interfacial free energy which corresponds to the process of adherence (ΔG_a) was calculated from values in Table 2 (Table 3). There is a weak correlation between the difference of adherence of *C. albicans* cells to latex rubber and silicon, and their corresponding ΔG_a 's. ΔG_a 's of adherence of *C. tropicalis* do correlate with the adherence of this fungus to both materials.

Depressed adherence of *C. albicans* was observed after urine treatment of silicon. However, urine treatment hardly altered the adherence of *C. albicans* to latex rubber (Table 4).

Soaking latex rubber in PBS resulted in an elevated adherence of *C. albicans* and a decrease of the contact angle. However, adherence of fungi to silicon, and their contact angle on it were not affected by soaking in PBS. On examining the PBS-induced change in latex, a release of substance(s) from the latex to the PBS was detected photometrically. An increase of absorbance (at 210 and 280 nm) by the aqueous medium was observed during long-term soaking. A steep increase after one day, followed by a gradual increase for up to eight days at both wave lengths was observed (Fig. 3).

Table 1. Factors predisposing to candiduria ($\geq 10^4$ /ml) and clinical features in urological patients studied at Hiroshima University Hospital, Hiroshima, 1985.

Patients Age ¹⁾ Sex	Urological & other disease	Episodes of candiduria within one month in patients with indwelling catheters		Received antibacterial drugs within 1 month	Bacteriuria Species, CFU ²⁾ /ml	Symptoms	Prognosis of candiduria
		Location	Duration (days)				
M.S. 53 F ⁴⁾	Lt. hydro- nephrosis with UVJ ³⁾ stricture	Ureter	≥ 14	Norfloxacin	None	Pyuria	Persisted for 6 mos.
O.M. 77 M ⁵⁾	Neurogenic bladder Gastric carcinoma	None (self- catheterization)		Ofloxacin	<i>Enterococcus</i> & <i>K. oxytoca</i> , 3×10^8	Pyuria	Unknown
K.K. 84 M	After prostatectomy	Urethra	8	Ampicillin Cefmetazone Norfloxacin	None	Hematopyuria	Persisted more than 1 mo.
O.W. 74 M	Bladder carcinoma DM, chronic bronchitis & Hemi- paresthesia	Urethra	2	Fosfomycin	None	Hematopyuria	Persisted more than 5 mos.
O.I. 83 F	Irradiation cystitis DM & cervical carcinoma	Urethra	6	Fosfomycin Cefazolin	None	Fever & hematopyuria	Persisted for 1 mo.
K.M. 73 M	Bladder carcinoma Chronic hepatitis	Urethra	≥ 14	Fosfomycin Cefaclor Panimycin	<i>P. cepacia</i> , 10^5 /ml	Fever & hematopyuria	Persisted for 1 week
Y.S. 63 F	Bladder carcinoma & neurogenic bladder	None		None	<i>Enterococcus</i> , $\geq 10^5$ /ml	Pyuria	Persisted for 2 days
S.A. 52 F	Renal failure due to ureteral invasion of gastric carcinoma	Ureter & Urethra	≥ 14	Latamoxef	None	Fever & Pyuria	Unknown
K.S. 33 M	After diver- ticulectomy & nephro- lithotomy	Urethra	4	Cefazolin	None	Fever	Persisted for 1 week
K.T. 68 F	Neurogenic bladder Parkinson disease	Urethra	≥ 14	Cefmenoxime	None	Fever & Pyuria	Persisted more than 6 mos.

Abbreviations: ¹⁾ years old, ²⁾ colony forming units, ³⁾ ureterovesical junction, ⁴⁾ female, ⁵⁾ male

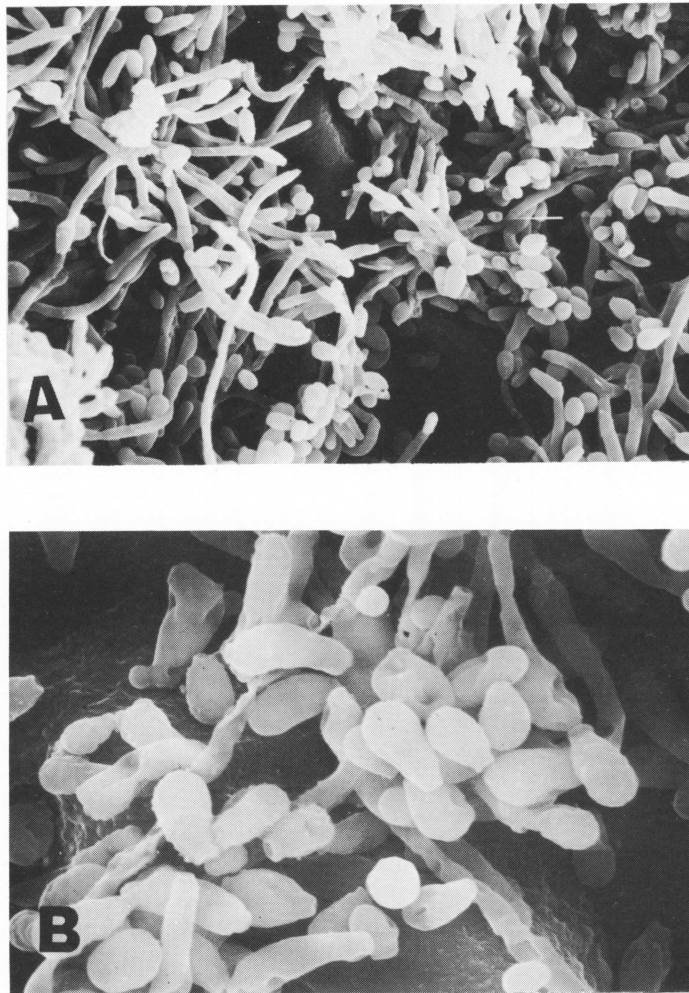


Fig. 1. Scanning electron micrographs of adherent fungi on the surface of a urinary catheter removed from a patient with urinary tract infection. Magnification (A) $\times 1,000$ (B) $\times 3,500$.

Table 2. Contact angles of distilled water on catheter materials and candidal layers

Material	Contact angle ^a (degree)	Surface free energy (ergs cm ⁻²) ^b	
		γ_{SV}^c	γ_{SL}^d
Silicon	113.8 \pm 1.7	14.33	43.71
Latex	104.4 \pm 2.4	19.33	38.60
<i>C. albicans</i>	51.1 \pm 1.9	52.60	22.81
<i>C. tropicalis</i>	118.6 \pm 4.1	11.70	46.48

^amean contact angle \pm the standard deviation.

^bsurface free energy was calculated from mean value of the contact angle.

^cfree energy of the surface.

^dinterfacial free energy between the surface and distilled water.

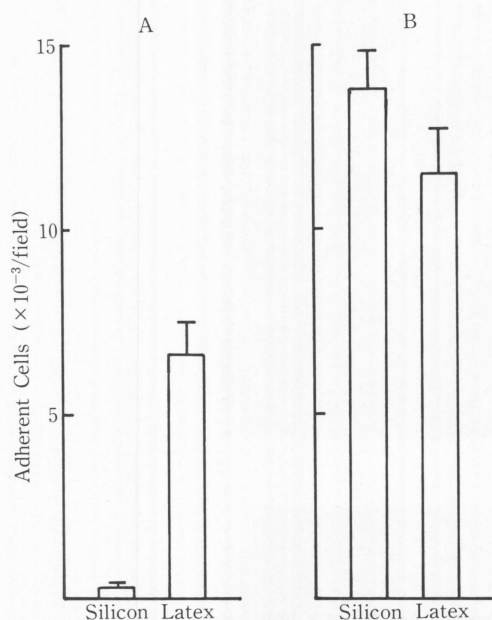


Fig. 2. Adherence of *C. albicans* and *C. tropicalis* to silicon and latex rubber catheter materials. Washed fungal cells were incubated with catheter material sheet at 37°C for 1 hr. Adherent cells in ten high power fields per sheets were counted. (A) *C. albicans*, (B) *C. tropicalis*.

Table 4. Effect of urine-treatment of the catheter materials on the adherence of *C. albicans*

Material	Number of adherent cells ^a	
	Non-treated	Urine-treated ^b
Silicon	289 ± 103	47 ± 16
Latex	9,742 ± 1,215	10,901 ± 1,392

^amean adherent cells per 10 fields of one sheet ± the standard deviation of five sheets.

^bsheets were incubated in human urine at 37°C for 1 hr.

Table 5. Changes adherence of *C. albicans* and contact angle on catheter materials by soaking in phosphate buffered saline

Material	Before soaking		After soaking	
	Number of adherent cells ^a	Contact angle ^b (degree)	Number of adherent cells ^a	Contact angle ^b (degree)
Silicon	314 ± 176	112.2 ± 2.6	533 ± 102	112.6 ± 1.5
Latex	7,054 ± 1,867	104.1 ± 2.2	31,642 ± 1,182	96.9 ± 2.5

^amean adherent cells per 10 fields of one sheet ± the standard deviation of five sheets.

^bmean contact angle ± the standard deviation.

Table 3. Change in interfacial free energy which corresponds to the process of candidal adherence to catheter materials

Fungus	Material	ΔG_a
<i>C. albicans</i>	Silicon	-28.25
	Latex	-28.74
<i>C. tropicalis</i>	Silicon	-87.56
	Latex	-76.85

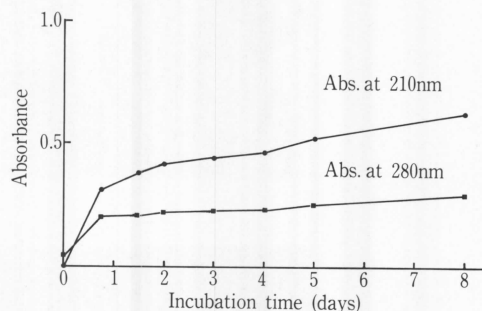


Fig. 3. Release of substance(s) from latex rubber catheter to aqueous medium. The release was followed by measuring the absorbance at 210 and 280 nm.

Various reagents were tested for their ability to remove adhered *C. albicans* from latex rubber sheets. Twenty millimolar ethylenediaminetetraacetic acid (EDTA), 1% Triton X-100 and 0.1% chlorhexidine removed 38, 28 and 32% of adherent fungi, respectively (Fig. 4). Among five *N*-acyl-phenylalanines tested, *N*-octyl-phenylalanine demonstrated outstanding ability in removing adherent *C. albicans*. Those acyl-phenylalanines with the acyl residue shorter than eight carbons had very weak *Candida* removing ability. Benzoic acid and phenylalanine, used as controls, did not remove fungi from catheter material sheets.

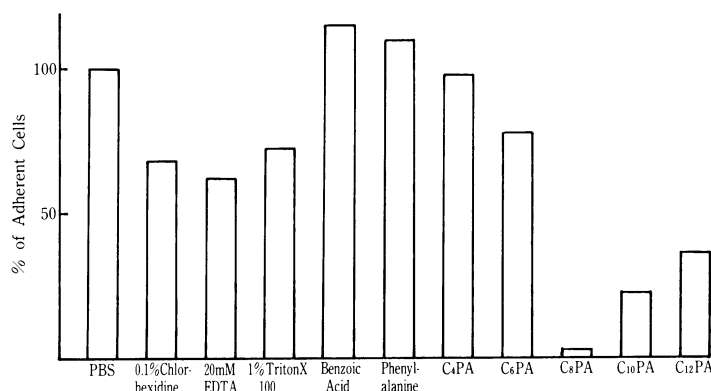


Fig. 4. Removal of adherent *C. albicans* from latex rubber catheter material. Latex sheets, to which *C. albicans* adhered, were incubated in various solutions. Fungal cells remaining on the sheets were counted and the percentage of control values calculated.

DISCUSSION

Candida is infrequently cultured from the urine of healthy subjects, because human defense mechanisms suppress its growth, and also because normal bacterial flora compete with it. However, since the advent and widespread use of antibiotics, immunosuppressive and anti-neoplastic agents, the frequency of *Candida* in the urine has dramatically increased^{2,28,34}. The clinical settings in which candiduria may present significant pathology are common. Although any chronically ill, debilitated patient is at some risk from candidiasis, several specific factors can be identified. One of them is indwelling catheterization. Harmony and Wezel¹¹, in comparing patients with hospital-acquired candiduria with case-matched controls, have noted a significant increase in the duration of prior Foley catheterization in those patients with candiduria. The first clinical rule in the management of candidiasis is normalizing the condition of the patient by removing iatrogenic factors. Therefore, it is worth studying the adherence of *Candida* to urinary catheters, since this is the first step in the candidal infection.

It is well-known that a greater amount of biofilm adheres to latex rubber catheter than to silicon catheters. In the present study, *C. albicans*, which is the most frequent fungus in human normal flora, was more adherent to latex rubber than to silicon *in vitro*. The cell surface of *C. albicans* has been reported to be hydrophilic^{17,18}. Therefore, we used *C. tropicalis*, whose cell surface is hydrophobic, to test the

participation of hydrophobic interactions in fungal adherence to urinary catheters. *C. tropicalis* adhered well to silicon, a hydrophobic material, whereas this fungus was less adherent to latex rubber, a hydrophilic material. Thermodynamical analysis of these data suggests that hydrophobic interactions are involved in the adherence of fungi to urinary catheters. Hydrophobic interactions have been reported to play an important role in the adherence of *Candida* to acrylic resin^{17,19}, and to intravenous catheters²², and of marine bacteria to plastic surfaces⁶. Although the relationship between the adherence of *C. tropicalis* to both materials and Δ Ga, and that of *C. albicans* to silicon agreed well with the data of Minagi et al¹⁷, *C. albicans* was, according to its Δ Ga, over-adherent to latex rubber. This indicates that other unknown factors may play a role in this adherence. Furthermore, long-term soaking of latex rubber in aqueous medium enhanced the adherence of *C. albicans* to this material. Our results indicate that substance(s), not yet identified, were released from the latex rubber into the aqueous medium, and this release changed the surface characteristics of the latex rubber, resulting in the enhanced adherence of *C. albicans*.

For treatment of urinary candidiasis caused by urinary catheters, the use of antifungal drugs is suggested. Imidazoles³⁶, ketoconazol¹⁰ and Amphotericin B³⁵ were tested for their therapeutic effects. *In vitro* studies demonstrated that the adherence of *Candida* to epithelial cells and to acrylic surfaces was decreased by antifun-

gal drugs^{16,29}). However, the use of antifungal drugs often causes severe side effects. Hence it is worth developing effective and safe bladder irrigating solutions for catheterized patients. In this study, we demonstrated that *N*-acyl-phenylalanines, especially *N*-octyl-phenylalanine, were highly effective in removing *Candida* from latex rubber sheets. *N*-Acyl-phenylalanines have characteristics as chelators as well as surfactants (Wu, W. 1985. Thesis). We also examined EDTA (a chelator), Triton X-100 (a surfactant) and chlorhexidine (an antiseptic). The discovery that none of them was as effective in removing adherent fungi as *N*-octyl-phenylalanine, indicates that the latter acts by a combined effect of its chelating, surfactant and perhaps as yet unknown actions.

N-Decyl-phenylalanine is added to suppository ampicillin to promote an absorbance from the rectum, and no reports of severe side effects are so far known. These facts suggest that *N*-acyl-phenylalanines could be used as excellent irrigating solutions of urinary tracts in patients with indwelling urinary catheters and associated candidal infections.

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