CLINICAL MICROBIOLOGY REVIEWS, Oct. 1995, p. 462–478 Vol. 8, No. 4
0893-8512/95/$04.00+0

New and Emerging Yeast Pathogens

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INTRODUCTION

In the fifth century B.C., Hippocrates described thrush (from reference 3) and, by doing so, was the first to describe a yeast infection. Microscopic detection of yeast cells in thrush did not occur until 1839 with the studies of Langenbeck and was subsequently confirmed by Berg and Gruby (from reference 3). Since then, the primary etiologic agent of thrush, *Candida albicans*, has been demonstrated to cause many forms of disease, some of which are life-threatening. *C. albicans* is the most frequently isolated yeast associated with human infections. Despite recognition of *Candida* species as agents of disease, little medical or scientific concern was given to them, in contrast to the many serious and highly prevalent bacterial infections recognized in the late 1800s. By 1963, approximately five medically important species of *Candida* had been described. The species were *C. albicans*, *C. stellatoidea* (which is now considered synonymous with *C. albicans*), *C. parapsilosis*, *C. tropicalis*, and *C. guilliermondii* (42). However, the advent in the 1960s of new modalities to treat cancer, increasing use of central venous catheters, an explosion in new antibacterial agents, increases in average life expectancy, and other developments in medicine soon paved the way for innocuous yeasts to cause serious infections. There are now at least 17 species of *Candida* that have been shown to cause disease in humans (127). With further developments in medical intervention and with the increasing population of patients who have immunodeficiencies or undergo transient or long-term immunosuppression, the list of yeasts that can cause disease continues to grow. This review is intended to summarize the clinical and microbiological information about these new and emerging yeast pathogens.

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DEFINITION OF NEW OR EMERGING YEAST PATHOGENS

Operationally defining a yeast species as a new or emerging pathogen is a subjective endeavor. Numerous problems affect how this decision is made. Yeast infections are not notifiable diseases, and therefore, no database in the United States or other country exists which allows comparisons of specific yeast isolations from year to year. Case reports in the medical literature are an indication of emerging yeast infections, but the propensity to publish such reports is affected by the desire of investigators to write the reports, to confirm the species identification, and to submit reports on species for which one or two previous reports from other investigators have already been published. It is likely that the incidence of isolations and infections associated with unusual yeasts is significantly underreported. Further complicating the evaluation of the medical significance of unusual yeasts is the consideration that single reports describing several cases of infection by a novel yeast species do not necessarily indicate that a new yeast infection is emerging. A yeast species may be unusually abundant at the reporting institution, or the institution may have changed to a

new identification system that distinguishes the species. Single reports that compare yeast isolates obtained during two defined time spans must be assessed carefully. Yeast isolation and identification during the two time spans may be affected by laboratory (procedural and technical changes) and environmental factors. A "novel" yeast species may also be synonymous with a more common pathogenic yeast species (e.g., *Candida claussenii* and *Candida langeron* are considered synonymous with *C. albicans* [82, 164]).

Despite these concerns, it is clear that yeast infections are increasing. Nosocomial fungal infections rose from 2.0 to 3.8 infections per 1,000 discharges between 1980 and 1990 in the United States (16). *Candida* species had become one of the most common causes of nosocomial bloodstream infections by 1990 (15). The increase in fungal infections can be ascribed to many factors, such as immunosuppressive therapeutic regimens, long-term catheterization, broad-spectrum antibiotic use, and longer survival of immunologically compromised individuals. Accompanying the increase in fungal infections is the recognition that yeasts previously thought innocuous are capable of damaging the human body. Organisms that were once relegated to plant pathology or industrial use are now included as potential agents of disease. Yeasts previously recognized to cause disease rarely or only under specific conditions are now reported with increasing frequency. This review will focus primarily on the newer, previously rare, or innocuous organisms. Organisms such as *Candida parapsilosis* and *Cryptococcus neoformans* which were well established to cause disease in humans decades ago will not be extensively described.

Several other emerging yeast species, including *Blastoschizomyces capitatus*, *Candida tropicalis*, *Malassezia furfur*, *Trichosporon beigelii*, and *Phaeoannelomyces elegans* (its mold synanamorph is *Exophiala jeanselmei*), will be mentioned only briefly, as several excellent reviews have been published recently about them (51, 65, 72, 86, 88, 143, 149, 154, 155, 159). When appropriate, information comparing these organisms with other new and emerging yeasts will be presented. This review is based primarily on literature reports during the past decade. Non-English reports were generally not included.

Yeast-like organisms are also becoming recognized as emerging pathogens. These include the algae *Prototheca* spp. and the mold *Penicillium marneffei* (67, 146, 147). Both organisms produce yeast-like cells in the host, but neither is a yeast, and they will be excluded from this review. *Geotrichum* spp. (61), which can be confused with *Trichosporon* spp., are also not included in this review because they are molds and do not produce blastoconidial cells.

WHICH YEASTS ARE NEW OR EMERGING PATHOGENS?

Several investigators have attempted to determine the changing incidence of yeast infections in the hospital setting, particularly at tertiary-care hospitals. All of these investigations are based on retrospective review of laboratory isolates with or without correlation of clinical data during a particular time frame. In numerous instances, a review of isolates identified in the clinical laboratory has led to the suggestion that particular isolates are now emerging as potential pathogens without any evidence that such organisms have caused infection. When infection is considered, the term is usually not defined, leading to confusion about the significance of a yeast isolate. This problem is particularly true with fungemia. Several of the new and emerging yeasts have been obtained by blood culture. While the organism may be detected in blood, evidence supporting its involvement in a pathogenic process is not provided. In some cases, the basis for considering an organism as causing an infectious process is based on resolution of fever accompanied by sterility of blood without evidence of clearance of an infectious focus. Such evidence is suggestive that the blood isolate was the etiologic agent of fever, but it is not definitive.

TABLE 1. Trends in emerging yeast infections

Yr of review	Reference	Summary
1989	126	Considered *Malassezia* and *Trichosporon* as opportunistic yeasts of increasing importance (literature review)
1989	7	Considered *C. tropicalis*, *Malassezia* spp., *Hansenula* spp., and *T. beigelii* as opportunistic yeasts of increasing importance
1989	8	Found that spectrum of yeasts associated with cancer patients is changing and includes *T. beigelii*, *Saccharomyces* spp., *Torulopsis pintolopesii*, *Pichia farinosa*, and *Rhodotorula* spp.
1992	129	Reported that emerging yeasts are *Saccharomyces*, *Hansenula*, *Rhodotorula*, and *Malassezia* spp. and *C. glabrata* (literature review)
1993	16	Determined increase in nosocomial yeast infections between 1980 and 1990; found that *C. albicans* infections increased (52 to 60% of yeast infections) while those with other species decreased (21 to 16%); *C. glabrata* was second most common species
1993	22	Compared 15-month periods in 1987–1988 and 1991–1992 for changes in yeast isolations; *C. glabrata* isolations doubled and *C. krusei* isolations increased slightly; prevalence of *C. guilliermondii*, *C. lipolytica*, and *C. kefyr* increased

Despite the problems with retrospective reviews of laboratory isolation data, several organisms appear to be emerging as important pathogens (Table 1). In particular, *Malassezia*, *Rhodotorula*, *Hansenula*, and *Trichosporon* species represent the more frequent isolates, although the spectrum of organisms appears wider than in previous years. Three studies compared the percent representation of different yeast species over two time periods within the same hospital setting (16, 22, 119). In one case, the percentage of yeast isolates that were *C. albicans* increased (16), while in the other two studies, the percentage decreased (22). All three studies indicated that *C. glabrata* had risen in incidence. The results from a third study (119) suggest that the use of fluconazole may have contributed to a significant increase in the isolation from blood of *C. parapsilosis* and *C. glabrata* and a dramatic decrease in *C. albicans*. Isolation of other *Candida* species, such as *C. krusei*, *C. guilliermondii*, *C. lipolytica*, and *Candida kefyr*, along with other unspecified species had also increased (22). These results are reflected by the increase in case reports concerning new and emerging yeasts (Table 2).

Not surprisingly, retrospective reviews of bloodstream yeast isolates have demonstrated a preponderance of isolates belonging to the genus *Candida* (Table 3). When studies are limited to this genus, the most frequently isolated species are *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. guilliermondii*, and *C. krusei* (13, 15). This list closely resembles the list of known pathogenic *Candida* species in 1963 with the exception of *C. glabrata* (which was then known as *Torulopsis glabrata*). Thus, it appears that the emergence of other yeasts as potential bloodstream isolates is a reflection of the changes in medicine since the early 1960s. The other yeasts that are

TABLE 2. Examples of clinical reports or reviews on the new and emerging yeasts and yeast-like organisms[a]

Organism	References
Blastoschizomyces capitatus	33, 88, 117, 154, 155
Candida chiropterum	48
Candida ciferrii	34, 48
Candida famata	120, 141
Candida glabrata	52, 73
Candida guilliermondii	21, 36, 56
Candida haemulonii	50
Candida humicola	4
Candida kefyr	99
Candida krusei	10, 54
Candida lipolytica	162
Candida lusitaniae	14, 57, 130
Candida norvegensis	107
Candida pintolopesii	8, 78
Candida parapsilosis	32, 115, 131
Candida pulcherrima	118
Candida rugosa	38, 144
Candida tropicalis	11, 20, 51, 66
Candida utilis	5, 23
Candida viswanathii	132
Candida zeylanoides	31, 84, 158
Exophiala jeanselmei	53, 65, 85, 143
Hansenula anomala	6, 59, 106
Penicillium marneffei	63, 112, 146, 147
Pichia farinosa	8
Prototheca wickerhamii	62, 67, 133
Rhodotorula rubra	26, 70
Saccharomyces cerevisiae	29, 30, 43, 110, 138
Sporobolomyces sp.	17, 100
Trichosporon beigelii	9, 47, 154, 155

[a] This table is intended to provide some examples of clinical reports and reviews on emerging yeast infections from the past 10 years. It is not a complete list of all such reports and does not include non-English language reports.

becoming more frequently recognized as etiologic agents of bloodstream infections include *Hansenula anomala*, *Blastoschizomyces capitatus*, *Rhodotorula* spp., and *Trichosporon beigelii*. The change in frequency of isolation may also reflect the ability of clinicians and technologists to recognize a non-*C. albicans* isolate as an important opportunistic pathogen and the ability of contemporary blood culture systems and procedures to support the growth of the unusual yeast isolates (see below). The recent reviews demonstrate that the important yeasts in bloodstream infection remain *Candida* species.

ANATOMIC SITES ATTACKED BY YEASTS

C. albicans can attack nearly every organ in the body and cause a wide spectrum of clinical manifestations. *C. albicans* is the most common yeast species isolated from blood. For many of the new and emerging yeasts, bacteremia or catheter-associated infection is the primary or only manifestation of disease (Table 4). However, several species appear to cause disease primarily at sites other than blood. For example, *Candida ciferrii* and *Candida pulcherrima* are associated with nail infections, and *Candida zeylanoides* has been obtained from skin and nails as well as blood.

It is striking how commonly the bloodstream is involved in the new and emerging yeast infections, as is the common association of hematogenous and solid malignancies with the appearance of the unusual yeasts. In numerous cases, the organism was obtained on repeat blood culture, suggesting a constant shedding of organisms into the blood. What is the nidus for the organisms? Unfortunately, insufficient studies are available to assess the possible origin of the unusual yeasts. For the species that have been isolated rarely, risk factor analysis is not possible. From an epidemiologic standpoint, all of the new and emerging yeasts can be found in the environment (109, 153), and many of the *Candida* species and *Saccharomyces cerevisiae* can be isolated from human mucosal sites, especially the gastrointestinal tract and vagina (109, 138). If risk factor analysis for common candidemias can be extended to the other *Candida* species and non-*Candida* yeasts, then several factors appear to be particularly involved. These factors include broad-spectrum antibiotic use, antineoplastic agent use, administration of vancomycin, intravenous catheterization, and neutropenia and other immunodeficiencies (7, 68, 125). These factors then result in further alterations in innate and specific immunity. Catheterization results in disruption of the integrity of the cutaneous barrier, antineoplastic agents cause thinning of the protective mucous barrier of the gastrointestinal tract and further attenuation of immune cell function, and broad-spectrum antibiotics can lead to proliferation of yeast growth on mucosal surfaces.

When considered together, these factors suggest that disruption of the gastrointestinal tract may be the most important predisposing factor leading to the development of infection, particularly fungemia, by the unusual (and usual) yeasts. Badenhorst et al. (13) noted that two factors, broad-spectrum antimicrobial therapy and abdominal disorders, including laparotomy, appeared to be most often involved (47 and 94%, respectively) in the development of fungemia. Surveillance surveys typically may not demonstrate the presence of the unusual yeasts on skin, except in association with nails (4, 109, 153).

TABLE 3. Trends in bloodstream infections caused by yeasts

Yr of review	Reference	Summary and comments
1985	66	Studied only candidemia; frequency of species was *C. albicans* > *C. tropicalis* > *C. parapsilosis* > *C. glabrata* > *C. krusei* > other species
1986	102	Concerned with Virginia hospitals; found increase in *Candida* infections between 1978 and 1984 from 0.1 to 1.5 cases/10,000 patient discharges
1989	113	Ranked nosocomial bloodstream infections; from 1984 to 1988, *Candida* species changed from eighth to fourth most common agent of infection; genera of gram-negative bacilli are considered as individual categories
1991	15	*Candida* species are fifth leading cause of bloodstream infection in 1989 (up from sixth in 1980) if gram-negative bacilli are considered one group
1991	13	Survey of fungemia for 1989 in one hospital in South Africa found that 2.1% of blood cultures contained yeasts; these included *C. albicans* (42%), *C. tropicalis* (26%), *C. parapsilosis* (20%), *C. glabrata* (7%), *Hansenula* spp. (2%), *C. guilliermondii* (1%), and *C. krusei* (1%)
1992	28	Retrospective study in Indian teaching hospital; compared 5-yr periods 1980–1985 and 1986–1990; found 11-fold increase in candidemia; most common species isolated were *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *C. guilliermondii*
1992	93	Fungemia isolates in one hospital between 1984 and 1990; *C. albicans* > *C. tropicalis* = *C. glabrata* > *C. krusei* > *C. parapsilosis* = *C. guilliermondii*

TABLE 4. Clinical information associated with the emerging and new yeasts

Organism	Site infected or affected	Underlying conditions of patients[a]	Predisposing factors[b]	Reference(s)
Candida ciferrii	Nails, ear	Otomycosis, onychomycosis	None stated	48
	Nails	NIDDM, vasculopathies, valvulopathy	Nail trophisms	34
Candida famata	Catheter,[c] blood	CML (BMT)	Long-term catheter	141
	Uvea	Cataracts	Cataract extraction with implantation of intraocular lens	120
Candida glabrata	Various, especially urinary tract, mucosal areas, lungs	DM, solid tumors; rarely hematologic malignancies; malnutrition; neonate	Cannulas, valve grafts, catheters, vascular surgery, mechanical ventilation, gastric perforations	52, 73, 101, 137
Candida haemulonii	Toe skin, nails, blood	Diabetes or not indicated	Unknown	50
Candida kefyr	Blood, spleen, kidneys	Adenocarcinoma	Radiation chemotherapy	99
Candida krusei	Blood	HIV, leukemia, lymphoma, BMT	Neutropenia, immunosuppression, prophylactic fluconazole	54, 140, 165
Candida lusitaniae	Blood, catheter, central venous cannula, urinary tract	Leukemia, myeloma, BMT, cystitis	Immunosuppression, antibiotic therapy	19, 57, 92
Candida parapsilosis	Blood, intravenous catheter, Foley catheter, peritoneum	Low birth weight, ESRD, immunodeficiency	TPN, antibiotic use	39, 115, 139
Candida norvegensis	Blood, peritoneal fluid	ESRD (renal transplant)	Antibiotic use, immunosuppression	107
Candida rugosa	Blood, burn wounds, catheter	Leukemia, granulocytopenia, burns	Topical nystatin, antibiotic use	12, 38, 144
Candida pulcherrima	Nails			118
Candida zeylanoides	Groin	None	None implicated	158
	Nails	Papillomavirus infection or none	Estrogen cream (?), nail plate separation	31
	Blood, right knee	Scleroderma, gastrointestinal malabsorption, IDDM	Kidney-pancreas transplant, hemodialysis, TPN	18, 84
Hansenula anomala	Blood, cannula insertion site	Low birth weight	TPN	104
	Endocardium (aortic valve)	Drug addiction	IVDA, alcohol abuse	108
	Blood	AIDS, carcinoma, MS, pancreatitis, AML, MVA	PN, CVC, tracheostomy, IVDA, antibiotic use, gastrointestinal bleeding	6, 64, 71, 106, 128
Rhodotorula rubra	Blood, catheter site	ALL, AML, aplastic anemia, lymphoma, sarcoma	CVC	70
	Peritoneum	ESRD, renal dysplasia	CAPD	40
	Alveoli (allergic alveolitis)	None	Long-term environmental exposure	41
Sporobolomyces salmonicolor	Lymph node, bone marrow	AIDS	IVDA, PCP (?)	100, 116
Saccharomyces cerevisiae	Vagina	None	Recurrent vaginal candidiasis, topical antimycotics, urinary tract infection, multiple antibiotics	138
	Blood	AML, anemia (myelodysplastic syndrome)	Granulocytopenia or not stated	8, 110

[a] Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BMT, bone marrow transplant; CAPD, continuous ambulatory peritoneal dialysis; CML, chronic myelogenous leukemia; CVC, central venous catheter; DM, diabetes mellitus; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; IDDM, insulin-dependent diabetes mellitus; IVDA, intravenous drug abuse; MS, multiple sclerosis; MVA, motor vehicle accident; NIDDM, non-insulin-dependent diabetes mellitus; PCP, *Pneumocystis carinii* pneumonia; PN, parenteral nutrition; TPN, total parenteral nutrition.

[b] In some cases, particularly in patients with cancer, the predisposing factors leading to yeast infection can be numerous and manifold. Only a few of the predisposing factors are provided in these cases. Interested readers may find several reviews concerning predisposing factors of yeast infections in the literature (8, 16, 129, 152, 159).

[c] Unless otherwise specified, catheter refers to a long-term indwelling intravenous catheter.

However, a survey of hospital personnel demonstrated that greater than 70% of nurses and nonnursing hospital personnel harbored yeasts on their hands (142). The most frequently isolated organisms were *Rhodotorula* spp. and *C. parapsilosis*. The latter species has also been shown to frequently colonize the skin, particularly the subungual space (160). Whether such colonization contributes to the increased isolation of *C. parapsilosis* in nosocomial candidal infections and contamination of

irrigation fluids, hyperalimentation solutions, and catheters requires further study (25, 131, 160). When a catheter is shown to be contaminated with yeasts, peripheral blood cultures are negative, and no other nidus is apparent, then skin may be a possible source for the implicated yeast.

If these observations are corroborated by other studies, the importance of surveillance cultures of gastrointestinal sites may be significant. That is, it may be useful to survey the yeast strains associated with the gastrointestinal tract of an immunocompromised patient in order to predict the most likely agent that could cause subsequent infection. Preliminary screening may also help to determine the effective antifungal agent prior to development of serious infection. The implementation of surveillance cultures and subsequent microbiological work-up may be too expensive to perform except for a subset of patient populations.

HISTOPATHOLOGY

A limited number of studies have described the fungal cell morphology and the histopathologic appearance associated with the infections caused by the unusual yeasts. In many of these studies, the histopathologic appearance is described only in broad terms. For the descriptions that are available, their usefulness must also be judged with the understanding that host immunologic status will influence the histopathologic picture. Diagnosis of unusual yeast infections would be helped by systematic studies of the histopathology associated with them in humans. On the basis of the information presented in Table 5, several generalizations can be made.

Unlike active *C. albicans* infection, which is typified histologically by the presence of yeasts and pseudohyphae (at least at later stages of infection), several of the unusual *Candida* species appear to produce only yeast forms during infection (Table 5). Species that attack the nails, a site that has a temperature lower than 37°C, appear to produce yeasts and pseudohyphae. This observation suggests that pseudohyphal production does not require a temperature of 37°C. *C. glabrata* appears to produce only yeast forms, which is consistent with its previous designation as *T. glabrata. Candida famata* (previously designated *Torulopsis candida*) also produced only yeast forms, but the significance of this finding is limited because only one study is involved (120).

It is evident from Table 5 that the appearance of yeasts and pseudohyphae does not imply that the etiologic agent is *C. albicans. C. ciferrii* and several other uncommon species of *Candida* produce similar tissue forms. It is notable that *T. beigelii* and *B. capitatus* also produce blastoconidial cells along with hyphae (97, 156). These organisms can be differentiated from *Candida* species by the predominance of hyphae produced in comparison with pseudohyphae and the paucity of blastoconidial forms. The presence of arthroconidia provides further evidence that the etiologic agent is a *Trichosporon* or *Blastoschizomyces* sp. and not a *Candida* sp.

A significant range of histopathology is associated with the unusual yeasts (Table 5). Low-virulence organisms do not necessarily stimulate poor immune responses. A mild cellular reaction seen in response to a low-virulence organism, such as *C. guilliermondii*, may not indicate that the organism does not provide immune stimulation. In one case of infection with this organism (36), the patient suffered from aplastic anemia. Her hematocrit was low (15.6%), and her leukocyte count was only 2,400 cells per mm^3. Most significant was the observation that her bone marrow was hypocellular, lacking leukocyte precursors. The mild reaction to the organism is easily explained by the host's attenuated cellular immune capacity. The poor host response also explains how this low-virulence organism was able to establish infection. Another low-virulence organism, *C. parapsilosis*, can induce acute and chronic inflammatory responses. D'Antonio et al. (32) have noted that hepatic and splenic microabscesses are frequently associated with *C. parapsilosis* fungemia in patients with hematologic malignancies. These observations demonstrate that organisms which are infrequent agents of infection and typically cause only mild disease in most patient populations can, under appropriate conditions, cause serious infection.

In most cases of infection by the unusual yeasts, the histopathologic response is characterized as inflammatory or as an abscess. However, granulomatous responses may also be seen. This is true with *C. glabrata*, *E. jeanselmei*, and *T. beigelii* (Table 5). Because of the limited number of investigations, it is not clear that other yeasts (Table 2) can also elicit a granulomatous response in an immunocompetent patient. Surgical pathologists and cytopathologists should be alerted to the possibility that many yeast species may cause a granulomatous response, and thus this characteristic does not help narrow the differential diagnosis.

TREATMENT OF INFECTIONS DUE TO UNUSUAL YEASTS

Infections by the unusual and emerging yeasts are, as mentioned above, diseases of the immunocompromised. Improvement of the host immunological status is perhaps the most important method by which to prevent the development and bring about the resolution of yeast infections. Unfortunately, in many cases, intervention of this nature is not possible, necessitating alternative therapeutic modalities for an ongoing infection.

In the case of fungemia, it is necessary to determine the origin of the organisms that are being shed into the bloodstream. Whenever possible, amelioration of a gastrointestinal problem would likely lead to significant improvement in the patient suffering from candidemia, particularly if the offending organism has a low virulence potential and the patient can mount an immune response. While helpful, gastrointestinal remediation provides only one element of therapy when the yeast has seeded other organs. In this case, antifungal therapy and other steps must be considered.

Catheter Removal

When a catheter is an infectious nidus, the choice of implementing antifungal therapy in light of the possible toxicities associated with such therapy must be weighed against possible patient outcome with no therapy and/or removal of the catheter. Surgically implanted central venous catheters are expensive to remove and replace. For many patients, the catheter is needed to provide venous access for delivery of various agents, such as parenteral nutrition. It is therefore desirable to treat the patient with antifungal agents while keeping the catheter in place. However, this management strategy is inappropriate. Table 6 summarizes the results of treatment in patients with fungemia due to unusual yeasts. In approximately 31% of the indicated cases, the patients died before the infection resolved. At least 74 of the 104 patients (71%) had catheters in place. In several cases, information about the use of a catheter was not provided, but it is likely that many of the patients had catheters in place, given their underlying illnesses. Among the 40 cases for which indications about the treatment outcome were included, 32 (80%) were successfully resolved by removing the catheter. In 28 of these cases, treatment with antifungal agents,

TABLE 5. Tissue morphology and histopathology associated with emerging yeasts[a]

Organism	Site affected or studied	Histopathology	Fungal cell tissue morphology	Reference
Blastoschizomyces capitatus	Endocardium (prosthetic mitral valve)	NS	Septate hyphae with some dichotomously branching, occasional yeast cells; arthroconidial cells also present	117
	Vertebral body	NS	Septate hyphae	33
Candida ciferrii	Nail	NS	Pseudohyphae, yeasts in clusters	34
	Skin (tinea pedis)	NS	Pseudohyphae, yeasts in clusters	34
Candida famata	Uvea	Histiocytes, epitheloid giant cells containing melanin pigment, and few lymphocytes on posterior surface of posterior lens capsule	Yeast forms	120
Candida glabrata	Endocardium	Fibrinopurulent exudate	Yeast cell clusters	27
	Various	Mild chronic infiltrate with lymphocytes, macrophages to frank granulomatous reaction	Yeast forms	11, 137
Candida guilliermondii	Various organs but not lung	Little tissue reaction	Yeast forms	36
Candida kefyr	Kidney, spleen	NS	Hyphae and budding yeasts typical of *Candida* species	99
Candida lusitaniae	Kidney	Mononuclear infiltrate, neutrophils sparse	Organisms eosinophilic (H&E stain) with clear haloes, budding cells	57
Candida parapsilosis	Synovium	Acute and chronic inflammatory changes	NS	69
Candida zeylanoides	Nail	NS	Mycelial elements and yeast cells, some pseudohyphae	31
Exophiala jeanselmei	Soft tissue of forearm	Inflammatory infiltrate with plasma cells, lymphocytes, macrophages, multinucleated giant cells	Lightly pigmented brown hyphae on H&E	143
	Lung aspirate (also contained *Staphylococcus aureus* and *Haemophilus influenzae*)	Acute inflammation	Hyphae	85
	Cervical lymph node	Granulomatous changes with multinucleated cells, histiocytes, neutrophils, and loci of large numbers of eosinophils	Pigmented pale brown, septate hyphae; single yeast-like cells, chains of fungal cells	65
Hansenula anomala	Intravenous cannula insertion site	Abscess (microscopy not described)	Yeasts	104
	Aortic valve vegetation	NS	Yeasts, many intracellular	108
Sporobolomyces holsaticus	Skin	NS	Yeasts with single buds	17
Trichosporon beigelii	Skin nodule	Granulomatous inflammation	Hyphae and blastoconidia	97
	Maculonodular skin lesion (patient with ALL)	NS	Arthroconidia, blastoconidia, pseudohyphae	156

[a] Abbreviations: ALL, acute lymphocytic leukemia; NS, not stated; H&E, hematoxylin and eosin stain.

usually amphotericin B, was included. In one case of infection with *C. zeylanoides* (84), amphotericin B therapy alone did not prevent subsequent infections. Only upon removal of a contaminated Hickman catheter was complete resolution obtained.

While these results indicate that catheter removal is a frequent practice, whether it is necessary in all catheter-associated yeast infections is unclear. In two cases, one involving *H. anomala* (103) and the other *C. lipolytica* (157), the catheter was removed but evidence of infection continued. Addition of antifungal therapy was necessary to resolve the infections. Before general conclusions about the efficacy of catheter removal or "treating through the catheter" can be made, more extensive studies are needed. A recent multicenter trial suggests that host factors, including the presence of intravenous catheters, may be more important than the MICs of antifungal agents for predicting patient outcome (123, 124). However, it is likely that each catheter-associated yeast infection will need to be approached as an individual management problem.

For at least one unusual yeast, *Rhodotorula rubra*, the importance of catheter removal is being addressed. Kiehn et al.

TABLE 6. Summary of outcome of fungemia caused by various emerging yeasts

Organism	No. of cases	No. of deaths before resolution of infection	No. with long-term catheters[a]	No. of cases with resolution of infection			Patient characteristics[b]	Reference
				Catheter not removed	Catheter removed, no antifungal therapy	Catheter removed, antifungal therapy		
Candida famata	1	0	1			1	BMT	141
Candida glabrata	1	0		1			Vascular surgery	101
	2	1	0				Neonate	52
Candida guilliermondii	1	1	NS				Aplastic anemia	36
Candida kefyr	1	1	0				Adenocarcinoma	99
Candida krusei	4	3	2 (4?)			1	BMT, leukemia, lymphoma	54
	10	0	NS[c]				BMT, leukemia	165
Candida lusitaniae	1	1	0				Multiple myeloma	111
	1	0	1		1		Preterm newborn	168
	2	0	1 (2?)	1		1?	Leukemia	19
Candida norvegensis	1	1	NS				ESRD	107
Candida lipolytica	1	0	1		1[d]		Cholecystectomy	157
Candida parapsilosis	22	15	22	NS	NS	NS	Cancer	115
Candida rugosa	1	0	1			1	Hypotension	122
	9	4	NS				Burn patients	38
	1	0	1 (Port-a-Cath)			1	CF	12
Candida utilis	1	0	1			1	Hemophilia, neutropenia	5
	1	0	0				Alzheimer's	23
Candida zeylanoides	1	0	1	1			GI bleeding	84
	1	0	1		1		IDDM, renal Tx	18
Hansenula anomala	11	2	8	NS	NS	NS	Newborn, AML	59
	1	0	1			1	Lung carcinoma	64
	1	1	1				Acute pancreatitis	106
	1	0	1			1	TPN	37
	1	0	1			1	MVA	6
	1	0	1			1[e]	Leukemia	103
	2	0	2		1	1	Carcinoma	71
Rhodotorula rubra	22	0	22	5		17	Cancer, others	70
	0	0	1			1	TPN	26
Saccharomyces cerevisiae	1	0	NS				AIDS	135
	1	1	1				Renal failure	30
	1	1	1				Myelodysplastic syndrome	110

[a] The specific catheter types (Hickman, Broviac, etc.) are usually not indicated in the references. The typical descriptions were central venous catheter or intravenous catheter. NS, not stated.

[b] Abbreviations: AML, acute myelogenous leukemia; BMT, bone marrow transplant; CF, cystic fibrosis; ESRD, end-stage renal disease; GI, gastrointestinal; IDDM, insulin-dependent diabetes mellitus; MVA, motor vehicle accident; TPN, total parenteral nutrition; Tx, transplant.

[c] Although not specifically stated, it is likely that many of the cases of severe disease (e.g., BMT patients) had long-term venous catheters in place during their hospital stay.

[d] In this patient, the central venous catheter was removed but fungemia persisted for another 11 days. The patient's blood became sterile after resolution of thrombophlebitis and fever.

[e] The catheter was removed, but the infection did not resolve. Amphotericin B was then administered, and the infection resolved.

(70) described 22 patients who had evidence of fungemia due to *R. rubra*. All of the patients had catheters in place. Only two patients had illness complicated by neutropenia. Regardless of whether the catheter was removed, the patients recovered from the episode of fungemia. All patients from whom the catheter was not removed received antifungal therapy. Whether antifungal treatment alone would have been sufficient for all of the patients is not clear. This study highlights several considerations. The particular yeast in this study is a skin and environmental saprobe with low virulence. The authors note that previous reports document only one death associated with culture-proven *Rhodotorula* fungemia. The source of the organism was likely the skin, as opposed to the gastrointestinal tract for many candidemias. Only one patient had a positive peripheral blood culture. All positive blood cultures were otherwise obtained through the catheter. *R. rubra* is also susceptible to amphotericin B (see below). These results suggest that a firm conclusion about the utility of catheter removal for treat-

ment of *R. rubra* infection is difficult to draw. It is possible that, for this organism, either antifungal therapy or catheter removal may be sufficient. Such a limited approach may not be appropriate for other unusual yeasts.

Antifungal Therapy

The antifungal agents that are available for treatment of yeast infections at sites other than the skin, nails, or vagina are generally limited to polyenes, primarily amphotericin B, 5-fluorocytosine (5-FC), and the azoles, namely, fluconazole, itraconazole, and ketoconazole. New agents with different mechanisms of action are under development (60). The efficacy of these agents for treating the unusual yeasts is unknown because insufficient cases have been reported to provide useful guidelines. Attempts to obtain some indication of the appropriate therapy for an ongoing infection must be judged on the in vitro susceptibility of the organism.

Yeast susceptibility testing has not been standardized. In 1992, the National Committee for Clinical Laboratory Standards published a proposed standard for yeast susceptibility testing (105). The proposed method involves broth dilution in either small (<150 μl) or large (<1 ml) volumes. Further work is needed before the proposed standard becomes finalized. In many cases, the MICs of a particular antifungal agent for unusual yeasts have been evaluated either by the proposed standard or by the agar dilution methods (Table 7). When the agar dilution method was performed by different laboratories, it involved different media, making comparison of the data from laboratory to laboratory difficult: this problem argues for the need for a standardized method.

Despite the use of different methods, several important susceptibility patterns are emerging for the unusual yeasts. Amphotericin B may not be the agent of choice for infections caused by *C. lusitaniae*, *C. parapsilosis*, and *C. kefyr*, while it appears to be satisfactory for the other organisms. *C. tropicalis*, *C. rugosa*, and *T. beigelii* may display higher MICs while remaining susceptible. Two organisms, *C. guilliermondii* and *C. lusitaniae*, have been reported to develop resistance with treatment with amphotericin B (2, 36). *C. parapsilosis* may show tolerance to amphotericin B. Thus, its MIC of amphotericin B would suggest that it is susceptible, but the minimal fungicidal concentration, as evidenced by growth of organisms on standard solid media after exposure to the drug in the MIC test, may be more than 32 times higher than the MIC (134). *C. rugosa* exhibits differential susceptibility to the polyenes, amphotericin B, and nystatin. Dubé et al. (38) noted that *C. rugosa* became the most common agent of fungemia in their burn patients following the use of topical nystatin ointment for prophylactic treatment of burn wounds. The overall incidence of fungemia decreased, however. Upon susceptibility testing, it was noted that the *C. rugosa* isolates were generally resistant to nystatin (MIC, >18.5 μg/ml) but remained susceptible to amphotericin B (MIC, generally ≤1.16 μg/ml) and to fluconazole (MIC, ≤5 μg/ml). These data show that the mechanism of resistance to nystatin may differ from that for amphotericin B despite shared mechanisms of action (24, 58, 91).

The susceptibility of the emerging and unusual yeasts to azole antifungal agents is variable (Table 7). The bistriazole fluconazole appears by in vitro tests to be ineffective or marginally effective against *C. krusei*, *C. guilliermondii*, *H. anomala*, and *R. rubra*. Variable efficacy is evident with *C. glabrata*, *C. parapsilosis*, *C. rugosa*, *C. tropicalis*, *S. cerevisiae*, and *T. beigelii*. *C. krusei* also appears to be clinically resistant to fluconazole. The MIC patterns for itraconazole, a recently approved triazole, did not parallel the patterns obtained with fluconazole. In many cases, organisms that were generally resistant to fluconazole were more susceptible to itraconazole (e.g., *C. krusei*, *C. guilliermondii*, *R. rubra*, and *S. cerevisiae*) but at MIC levels that were higher than those for *C. albicans*. Two exceptions are *C. parapsilosis* and *C. tropicalis*. These results indicate that in vitro susceptibility testing should include both triazoles, i.e., one triazole cannot be used to predict the efficacy of a second triazole. Interestingly, many of the unusual yeasts appear to be susceptible to ketoconazole. Variable susceptibility, however, was obtained with *C. glabrata*, *C. parapsilosis*, and *B. capitatus*. De Gentile et al. (34) noted that an isolate of *C. ciferrii* which had been obtained from a case of toenail onyxis demonstrated variable susceptibilities to different azoles when tested by diffusion methods. The organism was susceptible to clotrimazole, ketoconazole, and econazole but resistant to itraconazole, fluconazole, miconazole, and bifoconazole. Additional studies to determine if this species characteristically displays differential susceptibilities are needed. Such information could be valuable for identifying the organism by using an antibiogram.

Many of the unusual yeasts appear to be susceptible to 5-FC, suggesting that the combination of amphotericin B and 5-FC may provide effective therapeutic management regimen. *T. beigelii* and *B. capitatus* appear generally resistant to 5-FC. *Candida norvegensis* appears to be susceptible to 5-FC but at levels higher than those of most of the susceptible yeasts.

MICROBIOLOGICAL IDENTIFICATION

Taxonomy

Binomial epithets for the unusual (and usual) yeasts change frequently as more definitive methods (vis á vis molecular methods) are developed to differentiate the organisms and because there is no official organization that approves the correct taxonomic description and classification of fungal organisms. Taxonomic affiliation and appropriate binomial epithets are decided by consensus, resulting in the use of multiple names for the same organism (see Table 8) when different authors disagree about an organism's taxonomic status (82, 89). Further complicating this problem is the use of anamorphic epithets for organisms that have a known teleomorph (e.g., *C. krusei* [anamorph] and *Issatchenkia orientalis* [teleomorph]). This practice will likely persist because many times the teleomorph of a yeast is not evident, making its anamorphic name seem more appropriate. Also, as many clinical mycologists are aware, fewer inquiries about the implications of an organism are likely when a well-known anamorphic genus epithet (e.g., *Candida*) is reported than when a seemingly arcane teleomorphic epithet (e.g., *Clavispora*) is used. For the clinician, name changes appear to serve no useful purpose.

Many of the unusual yeasts are affiliated with the division *Ascomycotina* and are heterothallic (Table 8), that is, mating requires the union of thalli of opposite mating types. The notable exception is the teleomorph *Sporidiobolus salmonicolor* (anamorph, *Sporobolomyces*), which belongs to the *Basidiomycotina*. The number of different teleomorphic genera represented by the various *Candida* species is striking and helps demonstrate how uninformative a form genus designation can be for those hoping to understand an organism on the basis of its taxonomic nomenclature.

Significant Laboratory Characteristics

The mycology laboratory is challenged by the identification of clinically significant unusual yeasts. Many laboratories now use some form of rapid multiple biochemical test system (e.g.,

TABLE 7. Antifungal antibiograms of new and emerging yeasts[a]

Organism	No. of isolates studied	MIC (μg/ml)					Method	Reference(s)
		Amphotericin B	Fluconazole	Intraconazole	Ketoconazole	5-FC		
Candida ciferrii	1	S	R	R	S (also clotrimazole)	R	"Diffusion"	34
Candida famata	3		Generally R (>12.5)[b]				Multiple methods BD	121
	1	0.8			0.78	0.2	AD or BD	141
	1	1.56	6.25[b]			0.2	AD	166
	1				<20			49
Candida glabrata	25	0.06–1.0	0.05–12.5	0.05–0.2	0.0037–0.12	0.12–4.0	AD	87
	NS	0.1–0.4			1–64[b]	0.05–1.56	BD	136
	63	0.5–20[b]	1.0–512[b]			0.06–2.0	CBD	114
Candida guilliermondii	1	"Develop R"			0.25	0.2	AD	36
	5	0.06–0.12	3.2–25[b]	<0.05–0.2	0.0075–0.06	0.24	AD	87
	10	0.25–2.0	4.0–64[b]			0.06–1.0	CBD	114
Candida kefyr	1	0.4					BD	134
	>100	0.09–>6.25[b]					Various	90
Candida krusei	24	0.5–4.0	8.0–>512[b]			0.12–64[b]	CBD	114
	9	0.5–2.0	10–40[b]				BD or AD	165
	43	0.06–2	0.05–>100[b]	<0.05–3.2	0.0037–0.25	0.12–4	AD	87
Candida lipolytica	9	0.313–1.25			0.078–0.313		BD or AD	157
Candida lusitaniae	7	0.39–6.3 (developing R)			0.18–6.3	0.05–0.18	BD	2
	6	0.1–20[b]				<0.03–>160[b]	NS	111, 168
	8	0.12–1	<0.05–1.6	<0.05–6.4	0.0037–0.12	0.12–1	AD	87
Candida norvegensis	2	0.39			0.78	25[b]	BD	2
	1	0.4–0.8			0.4–1.0 (over 10 days)	3.2–12.5[b] (over 10 days)	AD	107
Candida parapsilosis	105	0.5–>2.0[b]	0.25–>512[b]			0.12–256[b]	CBD	114
	33	0.025–>6.25[b]		0.063–>128[b]	<0.125–>64[b]	<0.025–>100[b]	Various	90
	19	0.12–1	<0.05–50[b]	<0.05	0.0037–0.12	0.25–0.5	AD	87
Candida rugosa	10	0.5–2.0	2.0–32.0[b]			0.12–2.0	CBD	114
	4	0.25–4.0[b]			<0.046–12.5	<0.078–6.25	BD	144
	10	0.58–1.16	2.5–20[b]		0.1–0.8	<10–>323[b]	BD	38
Candida tropicalis	86	0.25–4.0[b]	2.0–>512[b]			0.12–>512[b]	CBD	114
	74	0.12–2	0.05–>100[b]	<0.05–100[b]	0.0037–8	0.12–4	AD	87
Candida utilis	1	0.52					BD	5
	1	0.04	4				BD	23
Candida zeylanoides	3		4–8.0[b]		0.12–1.0	<0.13 (one isolate, >128)	BD	84
	1	S			S	S	DD	31
	1	S			S	S	DD	18
Blastoschizomyces capitatus	15	0.15–0.62			0.04–50[b]	0.04–>100[b]	BD	88
	1	0.78	25		1.56	100[b]	BD	33
Hansenula anomala	4	0.78–1.56	1.56–12.5[b]			0.2–0.78	BD and AD	166
	1 (MIC_{99})	3.13	6.25			12.5[b]	AD	64
	Various	0.039–1 (4 isolates)			0.08 (1 isolate)	0.015–>100[b] (5 isolates)	BD	71
	1	1.56		12.5	0.39	0.1	BD	59
Rhodotorula rubra	9	0.8–1.6	6.4–>100[b]	0.8–12.8[b]	0.4–0.8	<0.1	BD	70
Sporobolomyces salmonicolor	1	<0.14	<1.25		0.2		BD	100
Saccharomyces cerevisiae	20 (MIC_{90})	0.2	40[b]	1.56	0.78	0.31	BD	138
	4	0.156–0.312	0.09–0.78		0.04–0.78	0.04–0.35	BD	12
Trichosporon beigelii	4	2.0	4		0.5	32–>32[b]	NS	47
	1	0.08	10	0.15		>100[b]	BD	150

[a] Abbreviations: AD, agar dilution assay; BD, broth micro- or macrodilution assay; CBD, colorimetric microbroth dilution assay; DD, disk diffusion assay; NS, not stated; R, resistant; S, susceptible; MIC_{90}, MIC for 90% of isolates; MIC_{99}, MIC for 99% of isolates.

[b] These ranges suggest that some isolates of the species may be resistant to the antifungal agent.

TABLE 8. Taxonomic nomenclature and classification of new and emerging yeasts[a]

Anamorph (previous common or merged synonym)	Teleomorph (alternative epithet)	Homo- or heterothallic	Teleomorph taxonomic affinity
Blastoschizomyces capitatus (*Geotrichum capitatum*, *Trichosporon capitatum*)	*Endomyces* spp. (?)[b]		Ascomycetes
Candida ciferrii	*Stephanomyces ciferrii*	Hetero	Ascomycetes
Candida famata (*Torulopsis candida*)	*Debaryomyces hansenii*	Homo	Ascomycetes
Candida glabrata	Not known		
Candida guilliermondii var. *guilliermondii*	*Pichia guilliermondii* (*Yamadazyma guilliermondii*)	Hetero	Ascomycetes
Candida guilliermondii var. *membranaefaciens*	*Pichia ohmeri*	Hetero	Ascomycetes
Candida haemulonii	Not known		
Candida kefyr (*Candida pseudotropicalis*, *Candida macedoniensis*)	*Kluyveromyces marxianus* var. *marxianus*	Hetero	Ascomycetes
Candida krusei	*Issatchenkia orientalis*	Hetero	Ascomycetes
Candida lipolytica	*Saccharomycopsis lipolytica* (*Yarrowia lipolytica*)	Hetero	Ascomycetes
Candida lusitaniae (*Candida obtusa*, *Candida parapsilosis* var. *obtusa*)	*Clavispora lusitaniae*	Hetero	Ascomycetes
Candida norvegensis	*Pichia norvegensis*	Homo	Ascomycetes
Candida pintolopesii (*Candida slooffii*)	*Saccharomyces telluris*	Homo	Ascomycetes
Candida parapsilosis	Not known		
Candida pelliculosa	*Hansenula anomala*	Hetero	Ascomycetes
Candida pulcherrima	*Metschnikowia pulcherrima*	Hetero	Ascomycetes
Candida rugosa	Not known		
Candida tropicalis	Not known		
Candida utilis	*Hansenula jadinii* (*Pichia jadinii*)	Homo	Ascomycetes
Candida viswanathii	Not known		
Candida zeylanoides	Not known		
Penicillium marneffei	Not known		
Rhodotorula rubra	Not known		
—*(no anamorph)*	*Saccharomyces cerevisiae*	Homo	Ascomycetes
Sporobolomyces sp.	*Sporidiobolus salmonicolor*	Hetero	Basidiomycetes
Trichosporon beigelii (*Trichosporon cutaneum*)	Not known		

[a] Data are from references 74, 82, 94, 127, 161, and 167.
[b] Questionable classification.

Vitek Yeast Biochemical Card [BioMérieux Vitek Inc., Hazelwood, Mo.], API 20C [BioMérieux Vitek], Uni-Yeast Tek [Remel Laboratories, Lenexa, Kans.], ID 32C [BioMérieux Vitek], MicroScan Yeast Identification Panel [MicroScan, West Sacramento, Calif.], and others). These systems provide a convenient method for identifying many yeasts, but the databases for all of these systems have insufficient test strains of the unusual yeasts or lack the unusual yeasts altogether (*C. utilis* is a common problem). This difficulty is particularly evident when the specificity and sensitivity of the systems are tested with the more unusual yeasts. These difficulties are not simple to alleviate because manufacturers must anticipate which species may arise as new opportunistic pathogens following the commercial release of their system. Such prognostication is obviously impossible. However, the clinical laboratory can perform some relatively simple tests that can provide useful clues to identification (Table 9).

Yeast morphology on standard media. While it is frequently true that cellular morphology is not a useful clue for yeast identification because many yeasts look similar when grown on standard mycologic media (e.g., Sabouraud dextrose agar and potato dextrose agar), this characteristic of a yeast should not be ignored. *S. salmonicolor* produces an elongated cell, with the spore produced at the end of a denticle (*Sporobolomyces holsaticus* is shaped similarly but lacks the denticle). *Kloeckera* species produce a distinctive apiculated yeast form. *C. glabrata* yeast cells are generally smaller than those of *C. albicans* (and can be confused with yeast forms of *Histoplasma capsulatum* or *M. furfur*). *Blastoschizomyces* and *Trichosporon* spp. form predominantly hyphal cells. A compendium on yeast identifications, such as that of Kreger-van Rij (75), should be consulted for other helpful cellular morphologies.

Pigment production. Perhaps the most obvious clue to species identification is colony color. *Sporobolomyces* and *Rhodotorula* spp. produce carotenoid pigments, although some species of these genera may not produce pigments (103). *R. rubra* produces the carotenoid torularhodin. With carotenoid production, *S. salmonicolor* appears salmon, *S. holsaticus* is peach to salmon, and *R. rubra* is salmon or pink. Microscopic morphology could then sort out which species is likely involved.

Assimilation. Standard assimilation reactions may be sufficient to differentiate many of the unusual yeasts but may sometimes lead to equivocal results for the emerging yeasts. *C. lusitaniae*, *C. tropicalis*, *C. parapsilosis*, and *S. cerevisiae* may appear similar by assimilation reactions. If rhamnose assimilation is positive, then the result is indicative of *C. lusitaniae*. A positive raffinose result suggests *S. cerevisiae* (57). *C. ciferrii* is not easily differentiated from *Candida edax* or *Candida chiropterum*. However, *C. chiropterum* does not assimilate melibiose. *C. edax* assimilates nitrate, while neither *C. ciferrii* nor *C. chiropterum* is positive for this assimilation.

Additional assimilation reactions may be useful, particularly when a commercial assimilation system profile index indicates low selectivity or low specificity and other standard identification tests do not match the system's first choice. This problem was noted by Walsh et al. (157) for a case of fungemia. Initial testing suggested that the offending yeast was *Candida ingens*. Upon further testing, it was identified as *C. lipolytica. C. ciferrii*

TABLE 9. Distinguishing laboratory characteristics of new and emerging yeasts[a]

Species	CMA morphology[b]	Pellicle	Urease	Growth at 37°C	CHX resistance	Assimilation reactions									Fermentation						Sexual spores[c]	References
						Gl	Ga	M	Rf	Tr	Ri	In	La	Ni	Gl	Ga	La	M	Su	Tr		
Candida ciferrii	H, p-h	V	−	S		+	+	+	+	+	+	+	−	−	V	−	−	−	−	−	2/ascus, helmet or hat shaped	34, 48
Candida famata	Y	V	−	V	V	+	+	+	+	+	+	−	V	−	W (V)	V	−	V	V	W (V)	1–2/ascus, spherical with warts (difficult to see)	1, 76, 141
Candida glabrata	Y	−	−	+	−	+	−	−	−	+	−	−	−	−	+	−	−	−	−	+ or W	—	94
Candida haemulonii	Y	−	−	+	−	+	V[d]	+	−	+	+	−	−	−	+	−	−	−	+	+	—	1, 94
Candida guilliermondii	Branched p-h, whorls of blastoc.	V	−	+	V	+	+	+	+	+	+	−	−	−	+	V	−	−	+	+	Depends on variety teleomorph	1, 79, 94
Candida kefyr	P-m well developed, occ. blastoc. clusters	−	−	+	V	+	+	−	+	−	+	−	+ or S	−	+	+S	V	−	+		1–4/ascus, crescent to reniform, agglutinates on MEA	1, 151
Candida krusei	Extensive p-m, clusters + chains of blastoc., may have slender, elongate cells	+	V	+	−	+	−	−	−	−	−	−	−	−	+	−	−	−	−		1–2/ascus, spherical (difficult to induce)	81, 94
Candida lipolytica	Abundant p-m and true mycelium, small chains or verticils of blastoc.	V	+	−		+	− (+)	−	−	−	− (+)	−	−	−	−	−	−	−	−		1–4/ascus, spherical or hat shaped, protuberance on 1 or 2 ends	77, 157
Candida lusitaniae	Well developed p-m, branched chains of slender p-h with short chains of blastoc. at verticils	−	−	+	− (V)	+	V	+	−	+	+	−	−	−	+	V	−	− (+W)	+ or W		1–4/ascus, clavate on MEA	1, 35, 57
Candida norvegensis	Abundant p-h, some curved if long, light tan	+ (thin)	−	−[e]	−	−	−	−	−	−	−	−	−	−	− (+S)	−	−	−	−	−	1–4/ascus, hat shaped on acetate agar	79, 107
Candida parapsilosis	P-m with branched chains, elongated cells, clusters of round/oval blastoc. along p-h; giant cells possible	−	−	+	−	+	+	+	−	+	+ or S	−	−	−	+	V	−	− (+W)	− (+W)		—	94
Candida pintolopesii var. *pintolopesii*[f]	P-m absent or branched chains of ovoid cells	−	−	+		−	−	−	−	−	−	−	−	−	+	−	−	−	−		1–2/ascus, spherical to ovoid, rough to spiny	167
Candida pintolopesii var. *sloofii*[f]	Well-developed p-m, round clusters of blastoc.																					
Candida pulcherrima	Y (aerobic), p-m (anaerobic)	−	−	V		+	+	+	−	+	+	−	−	−	+	V	−	−	−		1–2/ascus, from chlamydospore, spherical with peduncle	96
Candida rugosa	Primitive, highly branched p-m, short p-h	+	−	+	−	+	+	−	−	−	V	−	−	−	−	−	−	−	−	−	—	94

Candida tropicalis	P-m, abundant, long, branched p-h with blastoc. as singles, short chains, or clusters; true mycelium possible	V	−	+	+V	+	+	+	−	+	−	−	−	−	+	+	−	+	V	+S	—	94
Candida utilis	Primitive p-m, short, coarse p-h, ovoid cells	− (if +, then thin)	−	+		− (or +)	−	+	+	+ (or −)	−	−	−	+	+ (or W)	−	−	−	+		1–4/ascus, hat shaped on MEA	5, 79
Candida viswanathii	P-h long, wavy, irregularly branched, chains of ovoid blastoc.	−	−	+		+	+	+	−	+	+	−	−	−	+	+W	−	+	+S or −	+S		94
Candida zeylanoides	P-m, curving p-h, spherical to elongate blastoc., single or clusters	−	−	−	−	+	V	−	−	+	V	−	−	−	− (or +W)	−	−	−	−	+S or −	—	94
Blastoschizomyces capitatus	True mycelium, annellocon. percurren (arthrocon.)		−	+ (up to 45°C)	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	—	33, 148
Hansenula anomala	Y or abundant branched p-h		−	V		+	V	+	V	+	V	−	−	+	+	V	−	V	+W		1–4/ascus, hat shaped	80
Rhodotorula rubra (salmon to pink)	Y or rudimentary p-m, occ. well-developed p-m or true mycelium	−	+	V	+V	+	V	V	+	+	+ (or −)	−	−	−	−	−	−	−	−	−	—	45
Sporobolomyces salmonicolor	Variable (none to true hyphae)	+V	+	− (or +)		+	V	− (or +)	V	+	+	−	−	+	−	−	−	−	−	−	Reniform ballistospores	46
Sporobolomyces holsaticus	True hyphae, sparsely septate, ballistospores at terminus		+	−		+	+S	+	V	+	+	−	−	+	−	−	−	−	−	−	Obovoid, pyriform, and reniform ballistospores	17, 44
Saccharomyces cerevisiae	Y to rudimentary p-h		−	+	−	+	V	V	V	V	−	−	−	−	+	V	−	V	V		1–4/ascus, spherical or short ellipsoidal (acetate agar)	167
Trichosporon beigelii	True mycelium, arthrocon. abundant and variable in size, few blastoc.		+	+	+	+ (few −)	+ (few −)	+ (−)	V	V	V	+	+	−	−	−	−	−	−	−	—	74

[a] Abbreviations: annellocon., annelloconidia; arthrocon., arthroconidia; blastoc., blastoconidia; CMA, cornmeal agar; Ga, galactose; Gl, glucose; h, hyphae; In, inositol; La, lactose; M, maltose; MEA, malt extract agar; Ni, nitrate; occ., occasional; p-h, pseudohyphae; p-m, pseudomycelium; Ri, ribitol; Rf, raffinose; Tr, trehalose; S, slow; Su, sucrose; V, variable; W, weak; Y, yeast; +S, positive, may be slow; +W, positive, may be weak; +V, typically positive, seldom negative.

[b] Morphology is assessed by Dalmau technique on CMA without Tween 80. In some cases, typical morphologies require 7 to 14 days to develop.

[c] On V-8 agar for ascomycetes.

[d] Two types have been identified (see reference 83 for distinguishing characteristics). Type I variably assimilates maltose; type II assimilates maltose.

[e] First isolated from human vaginal specimens, suggesting that the organism may be at least tolerant to 37°C.

[f] The two varieties of this species differ in their requirement for inositol. *C. pintolopesii* var. *slooffii* requires inositol for growth, while *C. pintolopesii* var. *pintolopesii* does not.

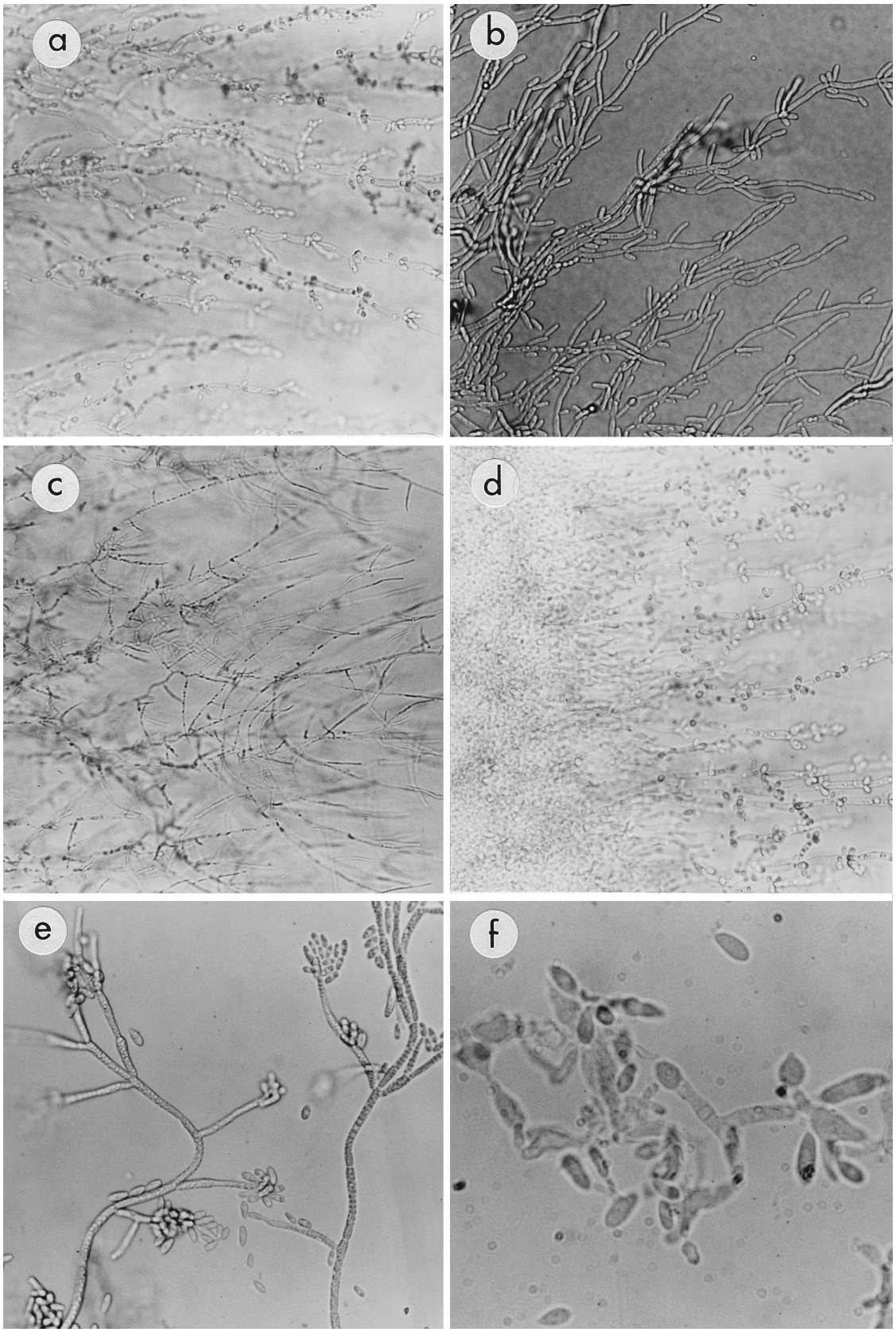

FIG. 1. Morphology of various unusual yeasts on cornmeal-Tween 80 agar: (a) *C. lusitaniae* (×250); (b) *C. kefyr* (×250); (c) *C. lipolytica* (×100); (d) *C. zeylanoides* (×250); (e) *B. capitatus* (×250); and (f) *S. salmonicolor* (×500). Photographs were generously provided by Davise Larone.

is unusual in that it can assimilate allantoin, inositol, adenine, and xanthine (95). *Trichosporon adeninovorans* and *Trichosporon terrestre* also assimilate adenine and xanthine but not allantoin, and *T. beigelii* assimilates inositol but is allantoin negative (74, 95). A recent report provides further differentiating characteristics for the *Trichosporon* species (55).

An organism that gives negative results on all assimilation tests may either grow too slowly for identification by the rapid assimilation systems or have a vitamin requirement. *Candida pintolopesii* var. *slooffii* requires inositol for growth, while *C. pintolopesii* var. *pintolopesii* does not. Vitamin requirements may also serve as important distinguishing characteristics for some yeasts; e.g., *C. lusitaniae* may be differentiated from atypical *C. tropicalis* by its vitamin requirements (145).

It is important to note that the assimilation profiles indicated in Table 9 are based on the results of the Wickerham assimilation method (163). It is possible that some of the reactions may not occur with the rapid commercial assimilation test systems.

Fermentation. Fermentation reactions are not usually tested in the clinical mycology laboratory, with the occasional exception of one or two sugars. These tests are helpful for identifying unusual yeasts and should be included along with assimilation reactions whenever possible. Fermentation reactions are usually slower than assimilation reactions and, for this reason, do not lend themselves to the rapid turnaround times that are desired by clinical laboratorians and physicians. Molina et al. (98) have developed a "rapid" (4-day) microfermentation system that could potentially find its way into the clinical laboratory.

Urease production. A positive urease test can provide a significant clue to the identity of an organism. Few nonbasidiomycetous organisms are urease positive. *C. krusei* strains vary in urease production, indicating that this species may actually be a complex of subspecies. *T. beigelii* is also urease positive, suggesting that it may have a basidiomycetous affinity.

Morphology on cornmeal agar with and without Tween 80. Depending on the species, a yeast will produce a number of forms when grown on cornmeal agar, especially if the medium is supplemented with Tween 80 (Fig. 1). True hyphae, pseudohyphae, arthroconidia, chlamydoconidia, and yeasts may all be formed. Among the unusual pathogenic yeasts, the production of true hyphae is characteristic of only a few organisms (Table 9). Many species produce pseudomycelium along with blastoconidia that emanate either from the junctions of catenated pseudohyphal cells or on the side of the pseudohyphal cells. The appearance of these structures at low magnification (100×) can be distinctive (e.g., a feather-like appearance for *C. zeylanoides*).

Nitrate assimilation. The very useful and rapid test for the presence of nitrate reductase is commercially available (Nitrate Swab-Rapid Test; Remel Laboratories). Only a few yeasts are able to assimilate nitrate (Table 9). Thus, a positive test provides significant information about the possible identity of an isolate and helps to rule out other organisms (e.g., *Cryptococcus albidus* versus *Cryptococcus neoformans*). If a false-negative result is suspected, a nitrate broth test should be used. Of the non-pigment-producing species listed in Table 9, *H. anomala* and *C. utilis* are the only nitrate-assimilating organisms.

CHX resistance. Resistance to cycloheximide (CHX) is, like the urease test, an extremely useful test for distinguishing yeast species. It can be easily determined by subculturing an isolate onto Mycosel (Difco Laboratories, Detroit, Mich.) or equivalent agar containing 400 to 500 μg of CHX per ml. However, some laboratories conduct the test with media containing 1,000 μg of CHX per ml (55). While the common *Candida* species that are isolated from patients are resistant to CHX, this characteristic is not shared by many of the unusual yeasts. The inability to grow in the presence of CHX implies that many of these unusual organisms may be missed by routine culture conditions. Infections at sites that are normally contaminated by other microbiota require that the laboratory use antibiotic-containing media in order to inhibit growth of bacteria. If the only antibiotic-containing medium used by the clinical laboratory has CHX, then the unusual yeast will not be isolated.

Growth at 37°C. All of the organisms discussed in this review have been associated with human infection, indicating that they are capable of at least tolerating and growing slowly at or near 37°C. As indicated in Table 9, several species do not grow well or do not grow at all at 37°C when tested under standard mycological test conditions.

Pellicle formation. Pellicle formation is easily evaluated by inoculating a glucose or other appropriate sugar assimilation tube with the yeast and checking for pellicle formation during the subsequent 7 to 10 days. Pellicle formation is not a rapid test but is useful when yeasts that are difficult to identify are isolated.

Ascospore production. A hallmark feature of fungi is the appearance and organization of their sexual structures. The teleomorphs of most of the unusual yeasts belong to the hemiascomycetes, indicating that no fruiting structure is made. The asci are considered naked. The size and appearance of the asci and the number and arrangement of the ascospores contained within them could provide substantial clues to the identity of the organism. A convenient medium for inducing sexual spore formation is V8 juice agar. Exceptions to this are indicated in Table 9.

Other methods. Various nontraditional methods are under development for the identification of yeasts. These methods require specialized and often relatively expensive equipment. Fatty acid analysis, rRNA sequence fingerprints, isoenzyme profiles, and random amplified polymorphic DNA assay profiles are examples of such methods. The next few years should prove interesting as these methods are investigated further.

CONCLUSIONS

C. albicans was once considered the only important yeast species associated with human infection. Modern medical therapy and improved methods for detecting and differentiating the yeasts have now shown that many other species are clinically important. During the past decade, it has also become apparent that species once considered only of industrial importance or innocuous inhabitants of the environment are capable of attacking the human host. These organisms can vary greatly in their susceptibility to the current antifungal agents, causing significant patient management problems. As more cases are reported and further developments in yeast identification procedures occur, the clinical microbiology laboratory and physicians will be better prepared to identify and treat infections with these unusual yeasts.

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