
The Pathogenic "Yeasts" Taxonomy*

Sexual Fungi (Teleomorphs/Holomorphs)

Hemiascomycotina
Heterobasidiomycotina/Holobasidiomycotina*
Yeast forms of Euascomycotina
(mostly dimorphic hyphal conidiogenous species*)
Yeast forms of some Zygomycota

Nonsexual Fungi (Anamorphs)

Fungi Imperfecti
Blastomycetes form-class members
Yeast forms of dimorphic Hyphomycetes form class members

*depending on authority

What are "Pathogenic Yeasts*?"

The "pathogenic yeasts"*** are most accurately defined as fungi that:

- grow predominantly by the vegetative reproductive process of budding
- may be monomorphic or dimorphic or polymorphic (pleomorphic)
- do not produce conidiophores or conidia (they are not yeast phases of Hyphomycetes members)
- tend to be asexual (but when sex is exhibited the majority are Hemiascomycotina members)

One major "pathogenic yeast" is a known, sexual Basidiomycota (Phragmobasidiomycetes/Tremellomycetes) member.***

* no strict definition

** is common jargon

*** sequencing also suggests that *Malassezia sp.* & *Trichosporon sp.* represent Basidiomycota members of the Ustilaginomycetes and Phragmobasidiomycetes classes, respectively.

Candidiasis*

Primary or secondary infection involving a member** of the form-genus *Candida*, particularly *C. albicans**** which may be mild, acute, subacute, chronic and episodic, and be cutaneous, mucocutaneous or systemic.

Generally, opportunistic infection that may range from mild irritation to a severe inflammation, and be chronic or acute suppurative disease that is rarely granulomatous.

Many systemic forms life threatening!

*#1 fungal public health problem

***C. tropicalis*, *C. krusei*[†], *C. parapsilosis*, *C. (T.) glabrata*?

***most are asexual members of form-class Blastomycetes (with Hemiascomycotina affinities)

+based on DNA homology, most strains may be *Issatchenkia orientalis*

Candida - most common form-genus of “pathogenic yeasts”*

1. *C. albicans* represents most common agent of mycosis
2. More form-species of *Candida* (and their teleomorph counterparts**) have been shown to be involved in more infections than those associated with any other form-genus
3. Many form-species are on body surfaces as “normal flora”

*gives rise to the multiple types of mycosis known as candidiasis

***Pichia*, *Lodderomyces*, *Kluyveromyces*, etc.

REVIEW
What are "Pathogenic Yeasts?"

The "pathogenic yeast" are most accurately defined as fungi that grow "predominantly" by the vegetative reproductive process of budding, may be monomorphic or dimorphic, but are mostly yeast forms of dimorphic or polymorphic fungi that do not produce conidiophores and conidia (they are not yeast phases of hyphomycetes), and tend to be asexual*, but when sex is exhibited, the majority are Hemiascomycotina members**; although one major "pathogenic yeast" is a known Basidiomycota member***.

Fungi Imperfecti

*Blastomycetes form-genera probable (based on sequencing) or known

<i>Candida</i>	Ascomycota** (all probable or known)
<i>Cryptococcus</i>	Basidiomycota*** (one known)
<i>Malassezia</i>	Basidiomycota (all probable)
<i>Trichosporon</i>	Basidiomycota (all probable)

**Ascomycota genera

Class

<i>Pichia</i>	
<i>Kluyveromyces</i>	Hemiascomycetes/Saccharomycetes
<i>Issatchenkia</i>	
<i>Debaryomyces</i>	
Etc.	

***Basidiomycota genus

<i>Filobasidiella</i>	Phragmobasidiomycetes/Tremellomycetes (controversial)
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Note: The Blastomycetes form genera listed are all included in the Form-family Cryptococcaceae.

Candidiasis

Ancient History -

Since antiquity - Hippocrates - "white mouth patches" - most likely thrush

Early "Modern" history (early, mostly European)

Veron - 1835; Thrush was acquired by newborns from mothers at birth

Berg & Bennett - 1840's; fungal etiology of thrush. Berg - inoculated babies with thrush membranous material → one death

Wilkinson - 1849; described vaginal candidiasis

Robin - 1850's; debilitation

- important to candidiasis
- thrush could become systemic

1940's → today: sustained rise in opportunistic cases (correlated first with rise in use of antibiotics, then with other medical treatments & conditions)

1980's → today: Same, plus AIDS disease

Candida & Candidiasis Survey Data*
(circa 1990 → present)

1. *Candida* carried in vagina by up to 35% of symptomless, normal women world-wide and rates increase with pregnancy, menstrual changes, oral contraception, etc.
2. Among nonpregnant women in U.S. with abnormal discharges, at least 20% have vaginal candidiasis
3. Among pregnant women with unusual discharge the rate is often in range of 30 -40%
4. Oral Thrush surveys in newborns show incidences of 0.5% →20% (average rate 4%)
Newborn Oral Thrush varies according to:
 - a. degree of maternal infection
 - b. maturity of infant at birth
 - c. method of feeding
 - d. social conditions
5. Fecal surveys indicate 10% → 85% of all individuals harbor gut flora that includes *C. albicans*
6. Sputum surveys show *Candida* isolations ranging from 0.5% to 77%**
7. Skin surveys show low but significant numbers of *Candida* can be isolated*** from skin surfaces of some normal individuals
8. *Candida* bloodstream infections occur at a rate of 0.5 to 2 per 1000 hospital admissions (& in 1990, comprised 10% of all nosocomial bloodstream isolates in U.S.)
9. The crude (overall) mortality varies among hospitals, but half studied series show rates of 35-55%
10. At the U. of Iowa Hospitals, the crude mortality rates for cases and matched controls were 57% and 19% respectively; thus, the attributable (direct) mortality due to candidiasis was 38%.
11. Risk factors associated with 10. were: # of antibiotics received prior to infection; isolates of *Candida* species from sites other than blood; prior hemodialysis, or Hickman catheter (note patient⁺ usually becomes systemically infected with own strain about 8 days after hospital admission; compromised).
12. Between 1980 & 1990, 27,200 of 344,610 (7.9%) of nosocomial pathogens (NNIS reported) were fungi & *Candida* accounted for 79% of these fungal pathogens.
13. *Candida* species in another study accounted for 5% of 9,704 blood stream infections (= to that of *E. coli*, > than *Klebsiella*)
14. Patients treated with cancer chemo-therapeutic agents or post-operative patients are at high risk if not treated immediately after detection of *Candida* in blood.
15. *Candida* infection remains as a clinical problem in AIDS patients, and the site of infection with *Candida* continues to predict progression of CD4 lymphocyte population depletion.
16. Oral AIDS center in San Francisco has demonstrated that erythematous and pseudomembranous oral candidiasis predict progression to AIDS in HIV+ at median of 25 months, and to death at 43 months.⁺⁺

*highly variable by reports

* *probably on high side

***contamination?

⁺this is controversial

⁺⁺w/o anti-HIV drugs

Probability of Nosocomial Candidemia in High-Risk Patients

- 1.7 times higher for each class of antibiotic received
- 7.2 times higher with Hickman catheterization
- 10.4 times higher with isolation of *Candida* from sites other than blood
- 18.1 times higher with acute hemodialysis

Factors that Favor Candidiasis

1. Extreme youth
2. Physiological changes
 - a. pregnancy (increased glycogen?)
 - b. steroids (also #4)
 - c. onset of puberty
 - d. extremes in diet
 - f. drugs
3. Prolonged administration of antibiotics
4. General debility and the constitutionally inadequate patient
 - a. avitaminosis
 - b. diabetes (increased blood glucose?)
 - c. cancer & its therapy
 - d. AIDS; 80-95% at some time during course, and other CMI defects.
 - e. Neutropenia
 - f. Corticosteroid/steroid therapy
5. Iatrogenic and barrier break procedures, e.g. catheters, dialysis, surgery, injections, wounds, burns, etc. (eg constant moisture)

Table 13.1 Clinical Forms of Candidiasis

"Superficial candidiasis" Overgrowth

- Cutaneous infection
- Chronic mucocutaneous infection
- Onychomycosis
- Oropharyngeal infection
- Vulvovaginitis
- Keratitis
- Conjunctivitis (inflammation of cornea & iris; inflammation of membrane lining eyelids)

"Deep candidiasis"

- Local inoculation
 - Esophagitis
 - Gastrointestinal candidiasis
 - Urinary tract infection [includes "fungus ball of the ureter," cystitis, renal abscess, & pyelitis (inflammation of pelvis, kidney)]
 - Peritonitis/intra-abdominal abscess

Hematogenously disseminated infection (fungemia)

- Candidemia
- Chronic disseminated ("hepatosplenic") candidiasis
- Suppurative phlebitis (inflammation of a vein)
- Endocarditis
- Meningitis
- Endophthalmitis (inflammation of inside of eye)
- Arthritis
- Osteomyelitis

K_C & B. p. 286

REVIEW

Summary of predisposing factors for invasive candidiasis

- Neutropinia (especially >7 days)
- Hematological malignancy
- Solid Tumor malignancy
- Postsurgical intensive care patients
- Prolonged intravenous catheterization
- Broad-spectrum or multiple antibiotic therapy
 - Parental nutrition
 - Severe burns
 - Neonates
- Corticosteroid therapy
- Intravenous drug therapy

Note absence of HIV+

Host Defense Mechanisms Against Disseminated Candidiasis

- **Phagocytosis by neutrophils and macrophages**
- **Defensins from granules in neutrophils**
- **Fungicidal agents excreted by monocytes and neutrophils into the immediate yeast cell microenvironment**
- **Cytoplasmic 30-kD protein, which inhibits *Candida albicans* growth, released by dying neutrophils**

"degenerated
heptaene"
6 = bonds

NYSTATIN
mycosamine (dideoxy-3-amino mannose)

Nystatin* - Traditional drug of choice for "colonizing/superficial" candidiasis

Nilstat - Lederle
Mycostatin - Squibb

1. oral tablets for recalcitrant intestinal and vaginal overgrowth*
2. powder - thrush as mouth rinse
3. ointment - cutaneous candidiasis e.g. Mycolog (Nystatin & Neomycin - Gramicidin - Triamei-
nalone Acetonide)
4. topical powder - *Candida* diaper rash
5. suppositories - rectal & vaginal overgrowths*
6. oral pill - intestinal overgrowth

***Mostly replaced by azoles, triazoles, imidazoles (EBIs)**

Treatment for Candidemia

Treatment of patients with positive blood cultures for *Candida* (New Recommendations, 1992, as per J. E. Edwards, Harbor UCLA Medical Center)

1. All patients with blood culture for *Candida* should be treated with antifungal whether or not culture associated with indwelling catheter and whether or not the diagnosis of disseminated candidiasis is or can be definitively established.
2. Until better data available treatment should be with amphotericin B until national recommendations with fluconazole, etc. clear.*
3. Less serious candidiasis in patients with low potential for systemic candidiasis can be treated with fluconazole/nystatin.

*controversial in sense that both very effective, maybe fluconazole 1st & save amphi- until needed or patient stronger (see text for other opinions).

Diagnosis

Hematogenously-spread candidiasis* remains difficult clinical diagnosis

1. No reliable serodiagnostic techniques available on a wide-spread commercial basis
2. Most helpful clues:
 - a. positive blood culture (however, often negative in certain systemically infected patient)
 - b. hematogenous *Candida* endophthalmitis (inside eye surface inflammation)
 - c. hematogenous *Candida* osteomyelitis (bone & bone marrow-associated inflammation; from CT)
 - d. candiduria in absence of instrumentation of the urinary tract.
1. Yeast culture and ID(?).

*Candidemia; candida fungemia

**Minimal Essential Information for
C. albicans ID (MEI)
(traditional)**

1. growth at 37°C
 2. negative capsule in India ink preps
 3. germ-tube formation in fetal calf serum (or selected substitutes)
 4. chlamyospore formation* and/or sucrose assimilation and/or etc.
- *Tween 80 agar

**Germ-tube Test
(traditional)**

~ 95% accurate for presumptive ID of *C. albicans*

media - ~ 0.5ml rabbit, fetal calf or human serum

inoculum - small numbers of young test organism (from isolation medium such as BHI or Sab)

incubation - 37°C for 2-3 hr

observation - yeast cells with germ tube

septum

vs

or

my* gt**

budding
yeast

pseudo-
hypha***

* mother yeast

**a hypha with parallel side wall in optical section and a down stream septum

*** chain of yeast cells that do not readily separate from each other