REVIEW ARTICLE

Yeasts in the Gut: From Commensals to Infectious Agents

Jürgen Schulze, Ulrich Sonnenborn

SUMMARY

Background: Controversy still surrounds the question whether yeasts found in the gut are causally related to disease, constitute a health hazard, or require treatment.

Methods: The authors present the state of knowledge in this area on the basis of a selective review of articles retrieved by a PubMed search from 2005 onward. The therapeutic recommendations follow the current national and international guidelines.

Results: Yeasts, mainly Candida species, are present in the gut of about 70% of healthy adults. Mucocutaneous Candida infections are due either to impaired host defenses or to altered gene expression in formerly commensal strains. The expression of virulence factors enables yeasts to form biofilms, destroy tissues, and escape the immunological attacks of the host. Yeast infections of the intestinal mucosa are of uncertain clinical significance, and their possible connection to irritable bowel syndrome, while plausible, remains unproved. Yeast colonization can trigger allergic reactions. Mucosal yeast infections are treated with topically active polyene antimycotic drugs. The adjuvant administration of probiotics is justified on the basis of positive results from controlled clinical trials.

Conclusion: The eradication of intestinal yeasts is advised only for certain clearly defined indications.

Key words: gastrointestinal mycosis, candidiasis, yeast infection, pathogenesis, treatment

Cite this as: Dtsch Arztebl Int 2009; 106(51–51): 837–42
DOI: 10.3238/arztebl.2009.0837

Nuthetal, Alice-Bloch-Straße: PD Dr. rer. nat. Schulze

Ardeypharm GmbH, Herdecke: Dr. rer. nat. Sonnenborn

Three decades ago, on the basis of case reports, the American physician C. O. Truss (e1–e3) proposed the hypothesis that an unhealthy lifestyle and increased intake of drugs, modified foods, and pollutants could lead to overgrowth of Candida species in the intestine. This would generally reduce the defenses of the host organism and trigger a multiorgan Candida-associated complex of symptoms ("Candida hypersensitivity syndrome"). Since then, this topic has been repeatedly and vigorously discussed by experts and laymen. In 1996, C. Seebacher even claimed that "mycophobia" was spreading. Many of the publications supporting Truss's hypothesis are not to be taken seriously. Abnormal conditions and severe diseases have often been uncritically linked to the mere detection of fungi in the gut, leading to the initiation of antimycotic therapy. This provoked justifiably critical publications during the 1990s, although some of these were exaggeratedly polemical (for example, e4). An objective scientific discussion on intestinal Candida colonization, with evaluation according to criteria of environmental medicine, was started in 2004, under the management of the Robert Koch Institute (1). Nevertheless, some questions remain open.

Since then, microbiological, molecular biological, and experimental clinical studies have succeeded in clarifying additional facts, so that it appears to be appropriate to re-evaluate the clinical importance of yeasts in the gut.

Methods

The report of the Commission on Methods and Quality Assurance in Environmental Medicine (*Kommission "Methoden und Qualitätssicherung in der Umweltmedizin")* on the Pathogenetic Significance of Candida Colonization of the Intestine appeared in 2004 (1). In order to identify later relevant literature, the database PubMed was searched and evaluated from 2005. The following search terms (MeSH) were used as selection criteria in the preparation of the present review article: "Candida/pathogenicity," "fungi/pathogenicity/virulence factors," "Candida/clinical trials, humans," "mycoses/microbiology/drug therapy AND gastrointestinal tract OR urogenital system." Publications on molds were not considered. Therapeutic statements are in accordance with national and international guidelines.

TABLE 1

Information on microorganism groups and counts in different sections of the gastrointestinal tract

Microorganisms	Stomach	Jejunum	Ileum	Colon
Aerobic and facultatively anaerobic microorganism groups				
Enterobacteria	$0–10^2$	$0–10^3$	$10^2–10^6$	$10^4–10^{10}$
Enterococci	$0–10^3$	$0–10^4$	$10^2–10^6$	$10^5–10^{10}$
Staphylococci	$0–10^2$	$0–10^3$	$10^2–10^5$	$10^4–10^7$
Lactobacilli	$0–10^3$	$0–10^4$	$10^2–10^5$	$10^6–10^{10}$
Fungi	$0–10^2$	$0–10^2$	$10^2–10^3$	$10^2–10^6$
Anaerobic microorganism groups				
Bacteroides spp.	rare	$0–10^2$	$10^3–10^7$	$10^{10}–10^{12}$
Bifidobacteria	rare	$0–10^3$	$10^3–10^5$	$10^8–10^{12}$
Anaerobic streptococci	rare	$0–10^3$	$10^2–10^4$	$10^8–10^{11}$
Clostridia	rare	rare	$10^2–10^4$	$10^6–10^{11}$
Eubacteria	rare	rare	rare	$10^9–10^{12}$

(Essential microorganism groups compiled as in [2].
Figures in colony forming units (CFU) per mL or per g intestinal content.

Intestinal microflora and fungi

Already at birth, microbial colonization starts in the gastrointestinal tract, which has previously been sterile. Intestinal microflora—now also known as microbiota—is established in successive stages and consists of numerous types of microorganism. More than 99% of this microbiota consists of bacterial and archaeal species (2). In addition, Candida yeasts are detectable in 96% of neonates by the end of the first month of life (e5). The constitutional development process is complete after 3 to 5 years and each individual then has an individual microflora compatible with his/her immune system. The special anatomical and physiological features of the individual compartments of the mouth, stomach and intestine offer disparate ecological niches and they are colonized with site-specific microbe communities (2).

Table 1 contains groups of important microorganisms detected by culture. The concentration ranges given for the individual counts of life microbes indicate the great individual variability in the microflora of adults. The findings also show that fungi are detectable in all gastrointestinal sections of about 70% of healthy adults (1). Most of these are members of the Candida genus. Normally 10^1 to 10^3 fungal cells per g stool are found, which is much lower than the corresponding values for bacteria – 10^{11} to 10^{12} bacteria per g stool. Fungi of other genera are occasionally detected in stool. Although these may be pathogens of the respiratory tract or skin, they are thought to be only transient in the digestive tract. Examples include Aspergillus, Mucor, Cryptococcus, Rhodotorula, and Trichosporon.

Even though Candida species are relatively often detected in stool, it is unclear whether these fungi are physiological and (useful) intestinal symbionts. As long as the site-specific microbial communities are intact and the innate immune system is functioning, Candida species behave like commensal members of the gastrointestinal microflora (3, 4, 5). They are then guests which cause no damage. For example, oral and esophageal candidiasis is only manifest when $CD4^+$ Th1 lymphocytes deficiency and reduced formation of proinflammatory cytokines (IL-12, INF-gamma) prevent effective defense against fungi (6, e6). Candida infections may arise as a consequence of

- disturbances in the host's defense systems, including the physiological intestinal microflora, the gut-associated immune system and the mucosa itself (4, 5, 7, e7);
- changes in gene expression in previously commensal Candida strains, including activation of virulence genes (8, e7–e9).

Janus-headed Candida

Candida spp. are yeasts which are normally present as individual cells and which predominantly replicate asexually by budding. The expression "yeast fungus" is pleonastic, as yeasts belong to the kingdom of the fungi. *Candida albicans* is a diploid polymorphic yeast with eight pairs of chromosomes. It can also replicate under anaerobic conditions, as found in the human colon (e8). Almost 200 Candida species are known, although few are important for man. The most important of these are *C. albicans*, *C. glabrata*, *C. krusei*, *C. dubliniensis*, *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii*, and *C. lusitaniae* (3, 4, e10). One reason that this list is short is that about two thirds of Candida species are incapable of growing at 37°C (e10). Molecular genetic studies have shown that there is much greater variety in individual Candida flora (e11).

Candida yeasts are classified as opportunistic pathogens, meaning that they are pathogens only under specific conditions (4, e7). Overgrowth of yeasts is normally inhibited by both specific (immune system) and non-specific defense systems (intestinal flora, peristalsis, intestinal enzymes, defensins, and others).

Changes in the qualitative or quantitative composition of the bacterial flora in the gastrointestinal tract—for example, after administration of antibiotics (9)—or a deficiency in specific parameters of the host's immune system evidently enhance the virulence of opportunistic Candida strains through gene regulation mechanisms (10, e7, e12). Their damaging activities can manifest at two different levels:

- Superficial infections of the skin, mucus membranes, or epithelia (skin or mucosal mycoses, Candida vaginoses)
- Invasive penetration into deeper tissue layers, distribution in blood and dissemination in various organs (invasive or systemic mycoses or candidoses).

Pathogenicity factors of Candida strains

Pathogenic yeasts bear genes coding for specific pathogenicity factors and for other properties important for the infection process (10, 11, e7). These primarily include adhesion factors, which mediate binding of yeasts to cell surfaces, such as epithelium or

endothelium, and aggression factors. The latter destroy tissues and include secreted aspartate proteinases, phospholipases, and lipases. Aggression factors are partially responsible for the invasiveness of fungi (e5). Strongly virulent Candida strains are capable of expressing several pathogenicity factors simultaneously (e10, e13–e15). Moreover, pathogenic yeasts have developed so-called escape mechanisms, to avoid the attacks of the immune system (6).

The first step in infection is interaction with the host cells by adhesion. *C. albicans* can express various adhesins, which bind to extracellular matrix proteins of mucosal or endothelial cells (12, e16). The close association with cell surfaces stimulates the formation of biofilms (e5). Biofilms are three dimensional consortia of microorganisms, which adhere to a surface and are enclosed by extracellular polymeric substances. Biofilm formation is directed by the emission and reception of signal molecules between the participating microorganisms ("quorum sensing") (e8, e14). One of the quorum sensing molecules used by Candida species is the oxylipin farnesol (e8, e17). The biofilm surrounds the yeast cells like a protective cocoon and largely keeps out attacks from the environment, including the immune system. In addition, resistance to antimycotics is enhanced by changes in metabolic reactions in the yeast cells within the biofilm (13). For example, so-called efflux pumps in the cell membrane are activated; these extrude absorbed antimycotics from yeast cells (e5, e14). Another example is the reduction in the synthesis of the cell membrane component ergosterol, which makes the yeast cells less sensitive to antimycotics by a factor of 30 to 2000 (13).

Ten different secreted aspartate proteinases (SAPs) are known for *C. albicans*. Depending on the situation, different tissue-specific SAPs are induced and these are important for the invasion of tissues and organs (4, 10, e18). Moreover, these Candida proteinases inactivate various host defense factors, such as immunoglobulins, complement factors and serum protease inhibitors, thus reducing opsonizing and microbicidal activity in blood. The term "phenotypic switching" means the rapid change in cell surface structure. This has been observed in some Candida strains and makes it more difficult for the immune system to recognize these yeast cells. It also seems to be associated with biofilm formation (14, e19–e21). During the reversible change from the roundish yeast cell shape to the protracted hyphae form *(Figure)*, the incorporation of beta-glucan molecules into the external wall layers is blocked (5). As a consequence, the pattern recognition receptors (toll-like receptors) of the innate immune system can no longer recognize the fungi or initiate an immune reaction, as they are "designed" for the recognition of the beta-glucan of the Candida cell wall (15, e5, e9, e22). The transition from the yeast to the hyphae form—and back—is controlled by various factors, including the synthesis of prostaglandins (PGE_2) and leukotrienes (LTB_4) (15, 16, e23–e26), or by contact with bacterial peptidoglycans (17). Any use of antibiotics leads to the release of peptidoglycans from the cell wall of intestinal bacteria, possibly thus increasing the formation of hyphae from *C. albicans* and enhancing its invasive potency (9).

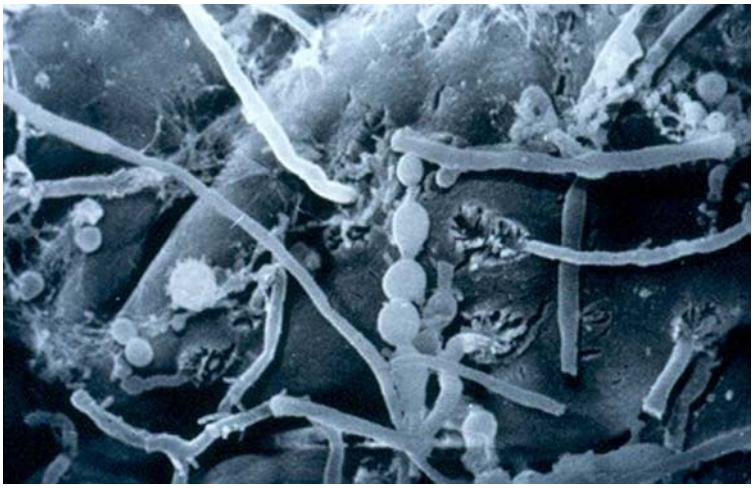

Figure: *Candida albicans* on human small intestine mucosa (biopsy material, scanning electron microscope image, 3000-fold magnification). Center of image: spherical budding cells; to the right and left of these: thread-like, aggressive fungal hyphae (taken by Ms A Lorenz, with kind permission of Ardeypharm GmbH)

Some Candida strains avoid the attacks of the immune system by concealing themselves in host cells. They can survive unharmed in epithelial cells (e27) or in non-activated macrophages (6, e28) and even replicate there.

As a result of transcriptional flexibility (11, e13), Candida species are extremely adaptable to the environmental conditions produced by the host, such as pH, partial CO_2 pressure, amino acid availability, and iron deficiency (8, 9, 18). The yeast genome can be slightly modified by repeated point mutations ("microevolution") and this can help the yeast to overcome the initial protective measures initiated by the host after the first contact (11). Moreover, chromosomal rearrangements can lead to the deletions of the chromosome sections mediating sensitivity to antimycotics. Recombination can also lead to the duplication of genes for efflux pumps, thus furthering the elimination of toxic substances.

Clinical significance of Candida infections

In contrast to other medically important fungi, such as Histoplasma capsulatum, Cryptococcus neoformans or Aspergillus fumigatus, human pathogenic Candida species are rarely found in environmental samples (4). In particular, *Candida albicans* is always associated with man or with warm blooded animals. Candida infections are contact infections. The pathogen reservoir is nevertheless not thought to be fungal spores, cells, or mycelium fragments taken up through the respiratory tract, but the Candida cells colonizing human mucosal surfaces, vaginal epithelium or skin—usually regarded as harmless commensals (7).

TABLE 2

Causes and predisposing factors for fungal infections

Causes	Factors (examples)
Physiological states with high susceptibility to fungi	Premature babies Neonates Elderly Persons during phases of hormonal adjustment (e.g. pregnancy, menopause)
Diseases, pathological conditions, operations	Hormonal diseases (e.g. diabetes mellitus, adrenal dysfunction) Immune deficiencies Infections Chronic inflammatory bowel diseases Hematological oncological diseases Malignant tumors Visceral operations Organ transplantation Alcoholism Bedridden patients
Therapeutic measures	Antibiotics Corticosteroids Immunosuppressives Intensive care Cytostatics Radiation Indwelling catheters

It is generally accepted that invasive candidoses are a real threat in hospitals. *C. albicans* is the yeast species most frequently isolated from clinical material and is involved in more than 50% of mucocutaneous and systemic yeast infections. On the other hand, there has recently been a clear increase in the proportion of non-albicans candidoses. Thus, infections with *C. glabrata* and *C. krusei* have increased more since 1990 than those with *C. albicans* (e29, e30). In the USA, for example, 11.5% of an approximate 80 000 blood infections per year are caused by Candida species. This is accompanied by a mortality rate of more than 30% (e31).

In many industrial countries, Candida mycoses are in fourth place among nosocomial infections in intensive care units (e31). Up to 20% of infections of medical implants, such as central venous catheters, bladder catheters or artificial heart valves, are due to infections with *Candida albicans* (e32). The predilection for forming biofilms on catheters and implants makes treatment with antimycotics enormously more difficult.

Table 2 lists predisposing factors for fungal infections, corresponding to the practical criteria of "very young, very old or very ill." Aside from oral soor, esophagitis and nappy rash, it remains unclear to what extent intestinal fungi are responsible for specific gastrointestinal diseases. Thus, Candida-associated infectious diarrhea has been frequently described in neonates, undernourished children, older patients, the severely or chronically ill, in intensive care units, or after long term antibiotic treatment (e33–e40). Nevertheless, these cases are rather rare in comparison to bacterial or viral intestinal infections.

Patients with irritable bowel syndrome most frequently suffer from intermittent persistent watery diarrhea, meteorism, flatulence, and abdominal pain—just the same as the dominant symptoms for patients with intestinal candidosis (e41). It is, however, unclear whether pathogenic yeasts are responsible for these symptoms in a proportion of patients with irritable bowel syndrome. A controlled study published in 1992 found no correlation between Candida colonization of the intestine and the symptoms of irritable bowel syndrome (e42). However, there are doubts about the quality of the methods used and there have been no more recent studies on this topic.

It has been known since the 1990s that *Candida albicans* may be involved in the occurrence of allergies. Thus, some cell wall components (mannans and mannoproteins) and enzymes (SAP, enolase) of *C. albicans* are potentially immunogenic and allergenic (19, e43–e50). Animal experiments have confirmed this association. *Canadida albicans* colonization of the mouse gut was promoted by antibiotic treatment. This enhanced pulmonary hypersensitivity towards nasally administered foreign protein (ovalbumin) or to spores of Aspergillus fumigatus. On the other hand, animals not colonized with *C. albicans* exhibited no hypersensitivity (16, e24).Moreover, *Candida albicans* provoked mast cell-mediated hyperpermeability of the intestinal mucosa in another mouse model (e51). The well known association between reduced barrier function of the intestinal mucosa ("leaky gut"), disturbances in the gut-associated immune system, changes in the intestinal microflora, and atopic diseases such as neurodermatitis, may bring special problems for patients with corresponding genetic susceptibility and intestinal *Candida albicans* colonization (19). However, this concept requires additional clinical studies.

According to current knowledge, all that remains of Truss's Candida hypersensitivity syndrome is the assumption of a relationship with the irritable bowel syndrome and the knowledge that Candida in the intestine may function as an "allergy trigger factor."

Therapeutic possibilities

Antimycotics of various substance classes are available for therapy as described in the guidelines. These may be administered orally or parenterally, depending on the localization and severity of the Candida infection (20, 21, e52, e53) *(Table 3)*.

Nystatin is the most frequently used non-absorbable antimycotic for candidoses of the orogastrointestinal tract. Orally administered topically active nystatin and systemically active fluconazole are also established components of the prophylaxis of Candida infections in the critically ill (22, e54, e55) and in premature babies (e56–e59). Nystatin—a polyene—is cheaper and has the advantage of causing fewer side effects than fluconazole—an absorbable azole derivative (e53, e60). There have been occasional reports of allergic reactions to nystatin (e61). Therapeutic failures may be due to decreased sensitivity or acquired resistance to azole

TABLE 3

Antimycotics and mechanisms of action

Substance classes	Active substance	Administration	Action on yeast cells
Antimycotics for mucocutaneous candidoses			
Polyenes	Nystatin	oral	Changes in permeability of cytoplasmic membrane from complex binding to ergosterol
	Natamycin	oral	Changes in permeability of cytoplasmic membrane by blocking ergosterol
	Amphotericin B	oral	Changes in permeability of cytoplasmic membrane from oxidative damage
Azole derivatives – Imidazoles	 Miconazole Ketoconazole	 oral oral	Damage to cytoplasmic membrane from inhibition of ergosterol biosynthesis
– Triazoles	Fluconazole Itraconazole Voriconazole	oral oral oral	Inhibition of 14-α-demethylase
Antimycotics for invasive candidoses			
Polyenes	Amphotericin B	IV	Changes in permeability of cytoplasmic membrane from oxidative damage
Triazoles	Fluconazole Itraconazole Posaconazole Voriconazole	IV IV IV IV	Damage to cytoplasmic membrane from inhibition of ergosterol biosynthesis Inhibition of 14-α-demethylase
Nucleoside analogues	5-fluorocytosine (5-FC, flucytosine)	IV	Inhibition of biosynthesis of RNA and DNA
Echinocandins	Anidulafungin Caspofungin Micafungin	IV IV IV	Incomplete cell wall synthesis due to inhibition of β-(1,3)-D-glucan synthase

(compiled from 20, 21, e52, e53)
IV: intravenous

antimycotics (20, e53). Care should be taken to avoid re-infections ("ping pong effect") by partner contact, or through dental prostheses, tooth brushes, mouthpieces, or dummies. Yeasts can however circumvent elimination by antimycotics by triggering the escape mechanisms we have described or by embedding themselves in biofilms. New therapeutic approaches are being discussed (5).

It is known that physiological intestinal microflora can provide protection against Candida infections in the orogastrointestinal tract (1, 3, e62). This focuses attention on probiotics. Twelve-month administration of a combination preparation with 8 bacterial strains to 10 pouchitis patients—in comparison to placebo therapy—gave the desired maintenance of remission and also significantly reduced the diversity of intestinal fungi ($p<0.002$) (e63). Controlled animal experiments have found that gastric ulceration promoted by Candida was attenuated after oral administration of L. acidophilus and was accompanied by more than 60% reduction in Candida colonization (23). A double blind placebo-controlled study with 80 premature babies found a significant reduction ($p = 0.01$) in intestinal Candida colonization after oral administration of L. rhamnosus for 12 months (24). An analogous study with 276 elderly patients and treatment for 16 weeks also found a significant decrease of Candida counts ($p = 0.004$) (25). Further controlled studies with probiotics are expected.

There are no reliable findings on the necessity for the adjuvant use of special nutritional forms ("anti-fungus diets"). It is much more sensible to use a—generally recommended—mixed diet with high fibre content and reduced sugar to stabilize the micro-ecological system in the gut.

Conflict of interest statement
Until 2005, Dr. Schulze was an employee of the company Ardeypharm GmbH. Dr. Sonnenborn is head of the section for biological research at Ardeypharm GmbH.

Manuscript received on 6 April 2009, revised version accepted on 14 September 2009.

Translated from the original German by Rodney A. Yeates, M.A., Ph.D.

REFERENCES

1. Kommission „Methoden und Qualitätssicherung in der Umweltmedizin": Pathogenetische Bedeutung der intestinalen Candidabesiedelung. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 2004; 47: 587–600.
2. Schulze J, Sonnenborn U, Ölschläger T, Kruis W: Probiotika. Mikroökologie, Mikrobiologie, Qualität, Sicherheit und gesundheitliche Effekte. Stuttgart: Hippokrates 2008; 4–16.
3. Bernhardt H, Knoke M: Mycological aspects of gastrointestinal microflora. Scand J Gastroenterol 1997; 32 (Suppl 222): 102–6.

KEY MESSAGES

- *Candida albicans* strains can in principle be classified as facultatively pathogenic yeasts.
- 10^2 to 10^4 CFU Candida are found per g stool in more than half the adult population, so that this cannot be equated with intestinal mycosis.
- Depending on the stability of the innate host barriers (mucosa, immune system, intestinal microflora), intestinal Candida colonization may lead to
  - superficial candidosis (restricted to the epidermal and mucosal surfaces),
  - locally restricted invasive candidosis, or
  - invasive systemic candidosis.
- The indications most closely linked to Candida colonization are irritable bowel syndrome and certain allergic reactions, although an association has been proven. There is no epidemiological or interventional evidence for the existence of a general and clinically demonstrable Candida hypersensitivity syndrome.
- Topically active antimycotics (such as nystatin preparations) are available for the treatment of superficial infections of the orogastrointestinal tract. Modulation of intestinal microflora with probiotics can suppress Candida colonization.

4. Hube B: From commensal to pathogen: stage- and tissue-specific gene expression of Candida albicans. Curr Opin Microbiol 2004; 7: 336–41.
5. Netea MG, Brown GD, Kullberg BJ, Gow NAR: An integrated model of the recognition of Candida albicans by the innate immune system. Nat Rev Immunol 2008; 6: 67–78.
6. Raska M, Belakova J, Krupka M, Weigl E: Candidiasis – Do we need to fight or to tolerate the Candida fungus? Folia Microbiol 2007; 52: 297–312.
7. Mathews HL, Witek-Janusek L: Host defense against oral, esophageal, and gastrointestinal candidiasis. In: Calderone RA (ed.): Candida and candidiasis. Washington: ASM Press 2002; 179–92.
8. Biswas S, Van Dijck P, Datta A: Environmental sensing and signal transduction pathways regulating morphopathogenic determinants of Candida albicans. Microbiol Mol Biol Rev 2007; 71: 348–76.
9. Piispanen AE, Hogan DA: PEPped up: induction of Candida albicans virulence by bacterial cell wall fragments. Cell Host Microbe 2008; 4: 1–2.
10. Thewes S, Kretschmar M, Park H, Schaller M, Filler SG, Hube B: In vivo and ex vivo comparative transcriptional profiling of invasive and non-invasive Candida albicans isolates identifies genes associated with tissue invasion. Mol Microbiol 2007; 63: 1606–28.
11. Morschhäuser J, Köhler G, Ziebuhr W, Blum-Oehler G, Dobrindt U, Hacker J: Evolution of microbial pathogens. Phil Trans R Soc Lond 2000; 355: 695–704.
12. Calderone RA, Fonzi WA: Virulence factors of Candida albicans. Trends Microbiol 2001; 9: 327–35.
13. Douglas LJ: Candida biofilms and their role in infection. Trends Microbiol 2003; 11: 30–6.
14. Soll DR: Phenotypic switching. In: Calderone RA (ed.): Candida and Candidiasis. Washington: ASM Press 2002; 123–42.
15. Bastidas RJ, Heitman J: Trimorphic stepping stones pave the way to fungal virulence. PNAS 2009; 106: 351–2.
16. Noverr MC, Falkowski NR, McDonald RA, McKenzie AN , Huffnagle GB: Development of allergic airway disease in mice following antibiotic therapy and fungal microbiota increase: role of host genetics, antigen, and interleukin-13. Infect Immun 2005; 73: 30–8.
17. Xu XL, Lee RTH, Fang HM, Wang YM, Li R, Zou H, et al.: Bacterial peptidoglycan triggers Candida albicans hyphal growth by directly activating the adenylyl cyclase cyr1p. Cell Host Microbe 2008; 4: 28–39.
18. Polakova S, Blume C, Zarate JA, Mentel M, Jorck-Ramberg D, Stenderup J, et al.: Formation of new chromosomes as a virulence mechanism in yeast Candida glabrata. PNAS 2009; 106: 2688–93.
19. Morita E, Hide M, Yoneya Y, Kannbe M, Tanaka A, Yamamoto S: An assessment of the role of Candida albicans antigen in atopic dermatitis. J Dermatol 1999; 26: 282–7.
20. Pappas PG, Rex JH, Sobel JD, et al.: Guidelines for treatment of Candidiasis. CID 2004; 38: 161–89.
21. Reinel D, Plettenberg A, Seebacher C, et al.: Orale Candidose. Leitlinie der Deutschen Dermatologischen Gesellschaft und der Deutschsprachigen Mykologischen Gesellschaft. JDDG 2008; 7: 593–7.
22. Cruciani M, de Lalla F, Mengoli C: Prophylaxis of Candida infections in adult trauma and surgical intensive care patients: a systematic review and meta-analysis. Intens Med Care 2005; 31: 1479–87.
23. Zwolinska-Wcislo M, Brozozowski T, Mach T, et al.: Are probiotics effective in the treatment of fungal colonization of the gastrointestinal tract? Experimental and clinical studies. J Physiol Pharmacol 2006; 57 (Suppl 9): 35–49.
24. Manzoni P, Mostert M, Leonessa ML, et al.: Oral supplementation with Lactobacillus casei subspecies rhamnosus prevents enteric colonization by Candida species in preterm neonates: A randomized study. Clin Infect Dis 2006; 42: 1735–42.
25. Hatakka K, Ahola AJ, Yli-Knuuttila, et al.: Probiotics reduce the prevalence of oral Candida in the elderly—a randomized controlled trial. J Dent Res 2007; 86: 125–30.

Corresponding author
PD Dr. rer. nat. habil. Jürgen Schulze
Alice-Bloch-Str. 7
14558 Nuthetal, Germany
JuR.Schulze@t-online.de

For e-references please refer to:
www.aerzteblatt-international.de/ref5109

REVIEW ARTICLE

Yeasts in the Gut: From Commensals to Infectious Agents

Jürgen Schulze, Ulrich Sonnenborn

E-REFERENCES

e1. Truss CO: Tissue injury induced by Candida albicans: mental and neurological manifestations. J Orthomol Psychiatry 1978; 7: 17–37.

e2. Truss CO: Restoration of immunologic competence to Candida albicans. J Orthomol Psychiatry 1980; 9: 287–301.

e3. Truss CO: The role of Candida albicans in human illness. J Orthomol Psychiatry 1981; 10: 228–38.

e4. Eckardt VF, Rösch W: Pilze im Darm. Krankheitserreger oder Kommensale? Dtsch Arztebl 1995; 92: A-2324–6.

e5. Kumamoto CA, Vinces MD: Alternative Candida albicans lifestyles: growth on surfaces. Annu Rev Microbiol 2005; 59: 113–33.

e6. Farah CS, Elahi S, Drysdale K, Pang G, et al.: Primary role for $CD4^+$ T lymphocytes in recovery from oropharyngeal candidiasis. Infect Immun 2002; 70: 724–31.

e7. Walker LA, MacCallum DM, Bertram G, Gow NA, Odds FC, Brown AJ: Genome-wide analysis of Candida albicans gene expression patterns during infection of the mammalian kidney. Fungal Genet Biol 2009; 46: 210–9.

e8. Kruppa M: Quorum sensing and Candida albicans. Mycoses 2008; 52: 1–10.

e9. Romani L, Bistoni F, Puccetti P: Adaptation of Candida albicans to the host environment: the role of morphogenesis in virulence and survival in mammalian hosts. Curr Opin Microbiol 2003; 6: 338–43.

e10. Calderone RA: Taxonomy and biology of Candida. In: Calderone RA (ed.): Candida and Candidiasis. Washington: ASM Press 2002; 15–27.

e11. Ott SJ, Kühbacher T, Musfeldt M, Rosenstiel P, Hellmig S, Rehman A, Drews O, Weichert W, Timmis KN, Schreiber S: Fungi and inflammatory bowel disease: alterations of composition and diversity. Scand J Gastroenterol 2008; 43: 831–41.

e12. Calderone RA: Virulence factors of Candida albicans. In: Calderone RA (ed.): Fungal pathogenesis: principles and clinical applications. New York: Marcel Dekker Inc 2001; 3–13.

e13. Magee PT, Chibana H: The genomes of Candida albicans and other Candida species. In: Calderone RA (ed.): Candida and candidiasis. Washington: ASM Press 2002; 293–304.

e14. Nobile CL, Mitchell AP: Genetics and genomics of Candida albicans biofilm formation. Cell Microbiol 2006; 8: 1382–91.

e15. Noverr MC, Huffnagle GB: Does the microbiota regulate immune responses outside the gut? Trends Microbiol 2004; 12: 562–8.

e16. Grubb SEW, Murdoch C, Sudbery PE, Saville SP, Lopez-Ribot JL, Thornhill MH: Candida albicans-endothelial cell interactions: a key step in the pathogenesis of systemic candidiasis. Infect Immun 2008; 76: 4370–7.

e17. Shea JM, Del Poeta M: Lipid signaling in pathogenic fungi. Curr Opin Microbiol 2006; 9: 352–8.

e18. Villar CC, Kashleva H, Nobile CJ, Mitchell AP, Dongari-Bagtzoglou A: Mucosal tissue invasion by Candida albicans is associated with E-cadherin degradation, mediated by transcription factor Rim101p and protease Sap5p. Infect Immun 2007; 75: 2126–35.

e19. Huang G, Wang H, Chou S, Nie X, Chen J, Liu H: Bistable expression of WOR1, a master regulator of white-opaque switching in Candida albicans. PNAS 2006; 103: 12813–8.

e20. Ramirez-Zavala B, Reuß O, Park YN, Ohlsen K, Morschhäuser J: Environmental induction of white-opaque switching in Candida albicans. PLOS Pathog 2008; 4: e1000089

e21. Zordan RE, Galgoczy DJ, Johnson AD: Epigenetic properties of white-opaque switching in Candida albicans are based on a self-sustaining transcriptional feedback loop. PNAS 2006; 103: 12807–12.

e22. Berman J: Morphogenesis and cell cycle progression in Candida albicans. Curr Opin Microbiol 2006; 9: 595–601.

e23. Noverr MC, Phare SM, Toews GB, Coffey MJ, Huffnagle GB: Pathogenic yeasts Cryptococcus neoformans and Candida albicans produce immunomodulatory prostaglandins. Infect Immun 2001; 69: 2957–63.

e24. Noverr MC, Noggle RM, Toews GB, Huffnagle GB: Role of antibiotics and fungal microbiota in driving pulmonary allergic responses. Infect Immun 2004; 72: 4996–5003.

e25. Carlisle PL, Banerjee M, Lazzell A, Monteagudo C, Lopez-Ribot JL, Kadosh D: Expression levels of a filament-specific transcriptional regulator are sufficient to determine Candida albicans morphology and virulence. PNAS 2009; 106: 599–604.

e26. Shen J, Cowen LE, Griffin AM, Chan L, Kohler JR: The Candida albicans pescadillo homolog is required for normal hypha-to-yeast morphogenesis and yeast proliferation. PNAS 2008; 105: 20918–23.

e27. Filler SG, Sheppard DC: Fungal invasion of normally non-phagocytic host cells. PLOS Pathog. 2006; 2: e129.

e28. Dalkilic E, Aksebzeci T, Kocatürk I, Aydin N, Koculu B: The investigation of pathogenity and virulence of Candida. In: Tümbay E, Seeliger HPR, Ang Ö (eds.): Candida and Candidamycosis. New York: Plenum Press 1991; 50: 167–74.

e29. Maschmeyer G: The changing epidemiology of invasive fungal infections: new threats. Int J Antimicrob Agents 2006; 27 (Suppl 1): 3–6.

e30. Tan TY, Tan AL, Tee NWS, Ng LSY: A retrospective analysis of antifungal susceptibilities of Candida bloodstream isolates from Singapore hospitals. Ann Acad Med Singapore 2008; 37: 835–40.

e31. Chauhan N, Latge JP, Calderone R: Signalling and oxidant adaptation in Candida albicans and Aspergillus fumigatus. Nat Rev Microbiol 2006; 4: 435–44.

e32. Nett J, Andes D: Candida albicans biofilm development, modeling a host-pathogen interaction. Curr Opin Microbiol 2006; 9: 340–5.

e33. Alam SA, Tahir M, De MN : Candida as a cause of diarrhoea in children. Bangladesh Med Res Council Bull 1977; 3: 32–6.

e34. Berkefeld I, Wahn V, Koletzko S: Candida-assoziierte chronische Durchfälle bei selektiv verminderter zellulärer Immunität gegen Candida. Monatsschr Kinderheilk 1991; 139: 528.

e35. Cimbaluk D, Scudiere J, Butsch J, Jakate S: Invasive candidal enterocolitis followed shortly by fatal cerebral hemorrhage in immunocompromised patients. J Clin Gastroenterol 2005; 39: 795–7.

e36. Danna PL, Urban C, Bellin E, Rahal JJ: Role of Candida in pathogenesis of antibiotic-associated diarrhoea in elderly in-patients. Lancet 1991; 337: 511–4.

e37. Gupta TP, Ehrinpreis MN: Candida-associated diarrhea in hospitalized patients. Gastroenterology 1990; 98: 780–5.

e38. Klingspor L, Stitzing G, Johansen K, Murtaza A, Holmberg K: Infantile diarrhoea and malnutrition associated with Candida in a developing community. Mycoses 1993; 36: 19–24.

e39. Mathaba LT, Paxman AE, Ward PB, Warmington JR: Genetically distinct strains of Candida albicans with elevated secretory proteinase production are associated with diarrhoea in hospitalized patients. J Gastroenterol Hepatol 2000; 15: 53–60.

e40. Micames CG, Bentley R, Onken J: Image 1—Invasive candidal enterocolitis. Gastroenterology 2007; 133: 391, 731.

e41. Bodey GP, Sobel JD: Lower gastrointestinal candidiasis. In: Bodey GP (ed.): Candidiasis : Pathogenesis, diagnosis and treatment. New York: Raven Press 1993; 205–223.

e42. Middleton SJ, Coley A, Hunter JO: The role of faecal Candida albicans in the pathogenesis of food-intolerant irritable bowel syndrome. Postgrad Med J 1992; 68: 453–4.

e43. Akiyama K, Shida T, Yasueda H, Mita H, Yamamoto T, Yamaguchi H: Atopic asthma caused by Candida albicans acid protease: case reports. Allergy 1994; 49: 778–81.

e44. Akiyama K, Shida T, Yasueda H, Mita H, Yanagihara Y, Hasegawa M, et al.: Allergenicity of acid protease secreted by Candida albicans. Eur J Allergy Clin Immunol 1996; 51: 887–92.

e45. Ito K, Ishiguro A, Kanbe T, Tanaka K, Torii S: Detection of IgE antibody against Candida albicans enolase and its crossreactivity to Saccharomyces cerevisiae enolase. Clin Exp Allergy 1995; 25: 522–8.

e46. Ito K, Ishiguro A, Kanbe T, Tanaka K, Torii S: Characterization of IgE-binding epitopes on Candida albicans enolase. Clin Exp Allergy 1995; 25: 529–35.

e47. Kanbe T, Utsunomiya K, Ishiguro A: A crossreactivity at the immunoglobulin E level of the cell wall mannoproteins of Candida albicans with other pathogenic Candida and airborne yeast species. Clin Exp Allergy 1997; 27: 1449–57.

e48. Savolainen J, Rantala A, Nermes M, Lehtonen L, Viander M: Enhanced IgE response to Candida albicans in postoperative invasive candidiasis. Clin Exp Allergy 1996; 26: 452–60.

e49. Savolainen J, Kosonen J, Lintu P, Viander M, Pene J, Kalimo K, et al.: Candida albicans mannan- and protein-induced humoral, cellular and cytokine responses in atopic dermatitis patients. Clin Exp Allergy 1999; 29: 824–31.

e50. Savolainen J, Lintu P, Kosonen J, Kortekangas-Savolainen O, Viander M, Pene J, et al.: Pityrosporum and Candida specific and non-specific humoral, cellular and cytokine responses in atopic dermatitis patients. Clin Exp Allergy 2001; 31: 125–34.

e51. Yamaguchi N, Sugita R, Miki A, Takemura N, Kawabata J, Watanabe J, Sonoyama K: Gastrointestinal Candida colonisation promotes sensitisation against food antigens by affecting the mucosal barrier in mice. Gut 2006; 55: 954–60.

e52. Morschhäuser J, Blum-Oehler G, Hacker J: Virulenz- und Resistenzmechanismen pathogener Candida-Spezies. Med Welt 1997; 48: 352–7.

e53. Segal E: Candida, still number one—what do we know and where are we going from there? Mycoses 2005; 48 (Suppl 1): 3–11.

e54. Normand S, Francois B, Dardé ML, et al.: Oral nystatin prophylaxis of Candida spp. colonization in ventilated critically ill patients. Intens Care Med 2005; 31: 1508–13.

e55. Wong PN, Lo KY, Tong GMW, Chan SF, Lo MW, Mak SK, et al.: Prevention of fungal peritonitis with nystatin prophylaxis in patients receiving CAPD. Perit Dial Int 2007; 27: 531–6.

e56. Isaacs D: Fungal prophylaxis in very low birth weight neonates: nystatin, fluconazole or nothing? Curr Opin Infect Dis 2008; 21: 246–50.

e57. Kaufman DA: Prevention of invasive Candida infections in preterm infants: the time is now. Expert Rev Anti Infect Ther 2008; 6: 393–9.

e58. Manzoni P, Leonessa ML, Monetti C, Farina D, Gomirato G: Prevention strategies in patients at high-risk for Candida infections: data from a neonatal intensive care setting. Intens Care Med 2006; 32: 936.

e59. Ozturk MA, Gunes T, Koklu E, Cetin N, Koc N: Oral nystatin prophylaxis to prevent candidiasis in neonatal intensive care unit. Mycoses 2006; 49: 484–92.

e60. Eggimann P, Wolff M, Garbino J: Oral nystatin as antifungal prophylaxis in critically ill patients: an old SDD tool to be renewed? Intens Care Med 2005; 31: 1466–1468.

e61. Martinez FV, Pamplona MPM, Garcia EC, Urzaiz AG: Delayed hypersensitivity to oral nystatin. Contact Derm 2007; 57: 200–1.

e62. Bengmark S: Ecological control of gastrointestinal tract. The role of probiotic flora. Gut 1998; 42: 2–7.

e63. Kühbacher T, Ott SJ, Helwig U, et al.: Bacterial and fungal microbiota in relation to probiotic therapy (VSL#3) in pouchitis. Gut 2006; 55: 833–41.