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Critical Reviews in Microbiology

ISSN: 1040-841X (Print) 1549-7828 (Online) Journal homepage: https://www.tandfonline.com/loi/imby20

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To cite this article: Louis Yi Ann Chai, David W Denning & Peter Warn (2010) *Candida tropicalis* in human disease, Critical Reviews in Microbiology, 36:4, 282-298, DOI: 10.3109/1040841X.2010.489506

To link to this article: https://doi.org/10.3109/1040841X.2010.489506

Critical Reviews in Microbiology, 2010; 36(4): 282–298

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REVIEW ARTICLE

Candida tropicalis in human disease

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Abstract

Candida tropicalis is one of the more common *Candida* causing human disease in tropical countries; the frequency of invasive disease varies by geography causing 3–66% of candidaemia. *C. tropicalis* is taxonomically close to *C. albicans* and shares many pathogenic traits. *C. tropicalis* is particularly virulent in neutropenic hosts commonly with hematogenous seeding to peripheral organs. For candidaemia and invasive candidiasis amphotericin B or an echinocandin are recommended as first-line treatment, with extended-spectrum triazoles acceptable alternatives. Primary fluconazole resistance is uncommon but may be induced on exposure. Physicians in regions where *C. tropicalis* is common need to be mindful of this lesser-described pathogen.

Keywords: Candida tropicalis*; candidiasis; candidosis*

Introduction

Non-*albicans Candida* species (NAC) are being increasingly reported as both colonizers and pathogens causing nosocomial fungal bloodstream infections (Pfaller et al. 2007a) and may account for almost 50% of all non-superficial *Candida* infections (Tortorano et al. 2006; Sobel 2006; Yang et al. 2009) the most common being *C. glabrata, C. tropicalis,* and *C. parapsilosis* (Tan et al. 2009; Sipsas et al. 2009). Traditionally *C. tropicalis* has been considered as second to *C. albicans* in terms of virulence and clinical importance though in recent years, epidemiological shifts have seen it being superseded by *C. glabrata* and other NAC in some institutions. In equatorial regions though, *C. tropicalis* remains a significant cause of yeast infections. However, relative to the wealth of information available on *C. albicans*, very much less is known about *C. tropicalis*. This paper reviews what is currently known about *C. tropicalis* and its role in human disease. Specific topics will be discussed, including its biology, epidemiology, pathogenesis, clinical perspectives especially infections in special patient groups, treatment, and antimicrobial resistance.

Literature search

Literature searches were done using the Pubmed gateway to access Medline (1966 to November, 2009). Keywords denoting *Candida*, *Candida tropicalis*, Candida identification, *Candida* typing, candidiasis, and candidosis were used. Additionally, we checked references from relevant publications and review articles to access articles published before 1966.

Biology and identification

C. tropicalis together with all other *Candida* species are members of the kingdom *Fungi*, of the division *Ascomycota*, class *Hemiascomycetes,* and order *Saccharomycetales* (Steffan et al. 1997). Traditional methods of systematics based on physical/morphological characteristics are being re-evaluated with increasing data from genomic sequencing for phylogenic analyses as one example illustrated in Figure 1 demonstrates (Fitzpatrick et al. 2006).

C. tropicalis is a diploid dimorphic yeast which exists as either ellipsoidal budding cells or as a pseudomycelium

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(Received 19 April 2010; accepted 26 April 2010)

ISSN 1040-841X print/ISSN 1549-7828 online
DOI: 10.3109/1040841X.2010.489506

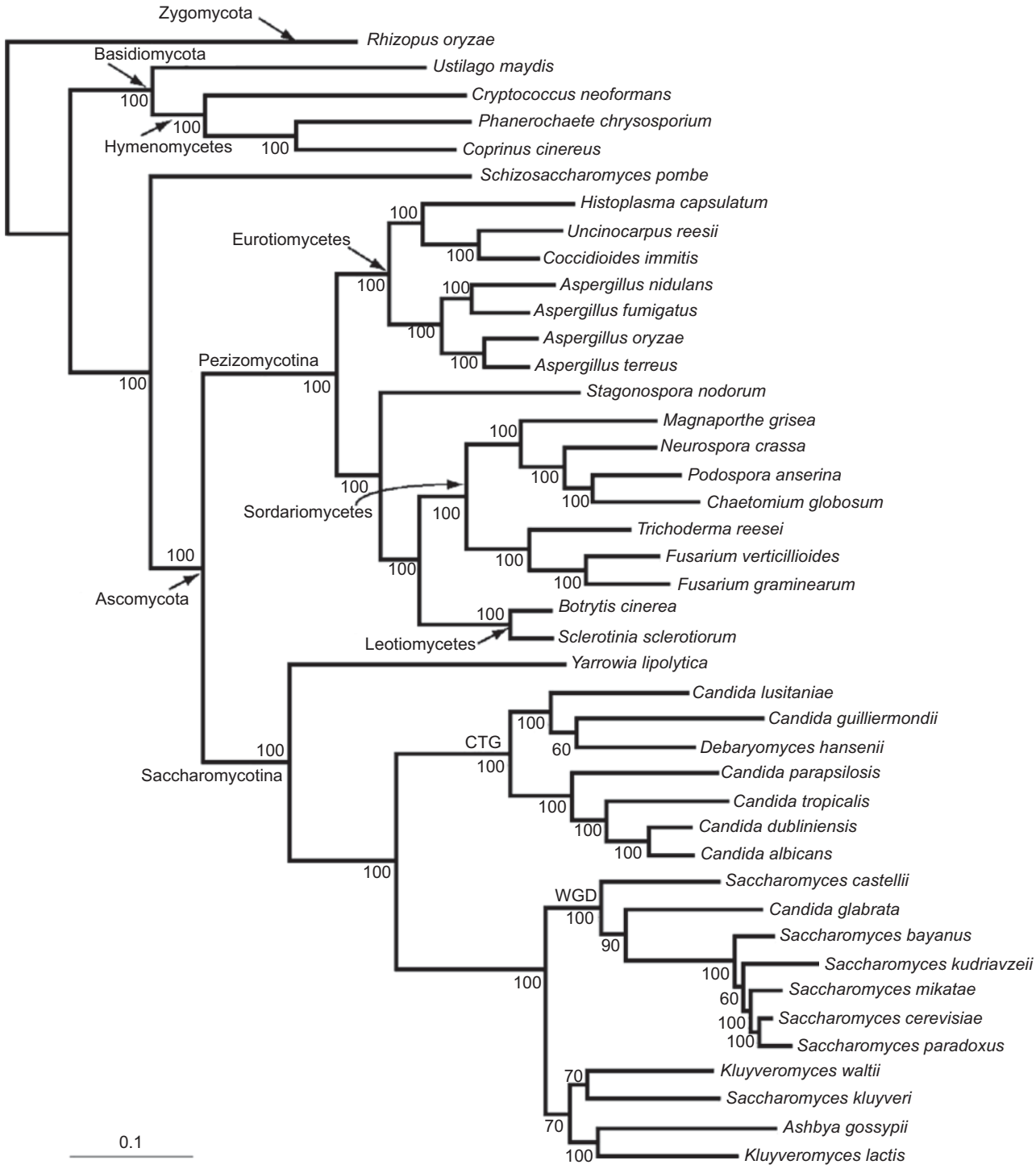

Figure 1. Example of fungal phylogeny based on combined gene analysis.

consisting of long, branched elements bearing conidia singly, in short chains or clusters. In rare cases *C. tropicalis* can form true hyphae, a property uniquely shared with *C. albicans* (Suzuki et al. 1991) (Figure 2).

Colonies on Sabourand or yeast potato dextrose agar are cream-colored or off white to grey, dull, soft, smooth, and creamy or wrinkled or tough. These colonies cannot be dependably distinguished from other *Candida* species based on macroscopic morphology or growth rate alone but are identified by the absence of terminal chlamydospores and a range of biochemical assimilation tests (Espinel-Ingroff et al. 1996). Commercially available chromogenic agars are available to assist in early presumptive identification of *C. tropicalis* from other *Candida* species:

CHROMagar™ Candida (CHROMagar Company Ltd) (Freydiere et al. 1997), Candida Diagnostic Agar (CDA) (PPR Diagnostics Ltd) (Cooke et al. 2002) and BiGGY agar. (Yucesoy et al. 2005) The former 2 are based on the ability of yeasts to hydrolyze either ß-glucosaminidase or indolyl glucosaminide substrates to colored end-products while the BiGGY agar utilizes the capability of *Candida* yeast in sulphite reduction. *C. tropicalis* colonies on CHROMagar™ *Candida* turn metallic blue after 24-72 hours incubation (Figure 3) (Odds et al. 1994), in contrast to *C. albicans* and C. *krusei* /other NAC which appear green and rose-colored respectively (Figure 4) (Hospenthal et al. 2006). On CDA *C. tropicalis* and *C. kefyr* appear pink with other species being white, yellow, or white with red spots (Cooke et al. 2002). *C. tropicalis* form dark brown/black colonies with a metallic sheen in BiGGY agar. Kit accuracy in *C. tropicalis* identification is variable, reportedly in the range of 73% to almost 100% (Cooke et al. 2002). Other media are available for to identify *Candida* from mixed populations including OCCA medium (Ozcan et al. 2009). Following presumptive isolation, a range of commercial kits are available for identity confirmation as required. These kits depend on assimilation of carbohydrates or hydrolysis of chromogenic substrates to distinguish from other *Candida* spp. (Lopez et al. 2005) API 20C (Figure 4) and API 32C AUX (bioMerieux France) have been widely used to characterize yeasts and correctly identify 90-95% of *C. tropicalis* as reported for API 20C (Heelan et al. 1998). Likewise, the Vitek yeast biochemical card has similar success in *C. tropicalis* identification though reading should ideally be performed at 48 hours to avoid early misidentification (Fenn et al. 1994). Current molecular diagnostics generally involves in-house PCR assays with internal validation and tends to be genus, rather than species-specific for *C. tropicalis* (Guo et al. 2006; Borman et al. 2008).

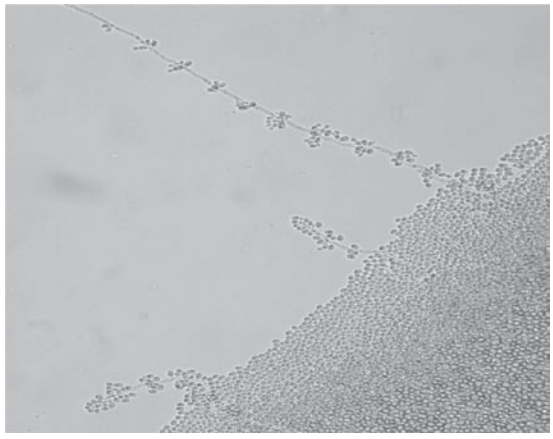

Figure 2. *C. tropicalis* pseudohyphae on cornmeal agar.

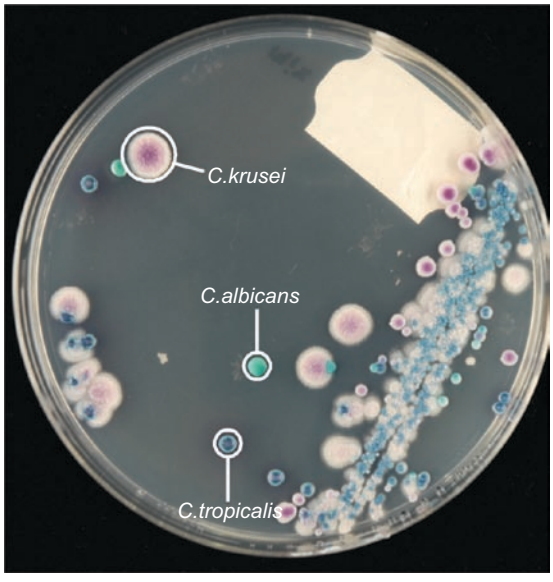

Figure 3. *Candida* spp identification using CHROMagar™ Candida identification plates.

The number of chromosomes and the genomic size of *C. tropicalis* are not known precisely, but pulse-field gels reveal approximately 5–6 pairs of homologous chromosomes and a genome size of ~30Mb (Doi et al. 1992). The *C. tropicalis* genome of strain MYA-3404 has been sequenced using whole genome shotgun technology (two plasmid libraries and a Fosmid library) as part of the Broad Institute Fungal Genome Initiative [*Candida tropicalis* Sequencing Project. Broad Institute of Harvard and MIT (http://www.broad.mit.edu)]. Prior to this, about 100 gene sequences of *C. tropicalis* were available in public databases corresponding to 60 different genes. The resulting 10X assembly was made public in January

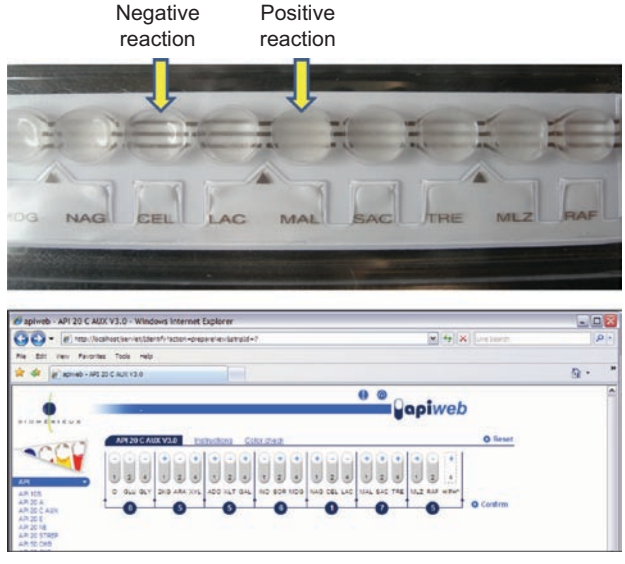

Figure 4. Biomerieux API 20C AUX strip identifies yeasts in 24–48 hours by assimilation test panels. Wells demonstrating turbidity greater than negative control are considered as positive.

of 2005. Initial automated analysis revealed a predicted proteome of 6,258 transcribed genes with a gene density of 62.1%. A random genomic library is also available and is composed of 1786 clones (average insert size 3.5 Kb) (Blandin et al. 2000). The guanine-cytosine content of nuclear sequences is 34.9%. (Blandin et al. 2000) have reported more than 1000 novel genes (from the analysis of 2514 random sequence tags) which have been deposited at EMBL with the accession numbers AL438875-AL441602.

Epidemiology

The incidence of bloodstream infections (BSI) caused by *Candida* species has risen 5–10 fold to become the fourth leading cause of nosocomial bloodstream infections (BSI) in developed countries (Wisplinghoff et al. 2004; Pfaller et al. 2001) with incidence rates of up to 20 per 10,000 hospital discharges in the US (Pfaller et al. 2007a). While *C. albicans* has remained the most common species causing invasive candidiasis worldwide, there is a trend towards decrease in isolation of *C. albicans* accompanied by an increase in *non-albicans Candida* between 1997-2003 (Pfaller et al. 2007a; Pfaller et al. 2007b). *C. tropicalis* represents 3–66% of all *Candida* bloodstream isolates worldwide (Viscoli et al. 1999; Pfaller et al. 2000; Sipsas et al. 2009; Yap et al. 2009; Yang et al. 2009; Sabino et al. 2009; Tan et al. 2009) and in many centers is the second most common *Candida* isolated. This variability in prevalence is subject to the geographical location: e.g. US hospitals 12–25%, European hospitals 4.5–9%, Brazil 20–24%, and South Asia, between 20% to more than 60% (Viscoli et al. 1999; Krcmery et al. 1999; Leung et al. 2002; Pfaller et al. 1999; Tortorano et al. 2002; Slavin 2002; Nucci et al. 2007; Yang et al. 2009; Sipsas et al. 2009). The relatively lower frequency of *C. tropicalis* infections in some developed countries of the West (in which *C. glabrata* is emerging as second in importance to *C. albicans*) should not detract attention away from *C. tropicalis* as the latter has a notable prevalence in tropical climates and has a predilection to cause disease in certain patient groups.

It is notable that equatorial countries in South Asia (India, Thailand, Singapore, Thailand) and Brazil (Foongladda et al. 2004; Goldani et al. 2003; Gupta et al. 2004; Wang et al. 2004; Cheng et al. 2006; Tan et al. 2009) have reported a high frequency of *C.tropicalis* BSI (Viscoli et al. 1999; Leung et al. 2002; Pfaller et al. 1999; Tortorano et al. 2002; Slavin 2002). The tropical climate, temperature and humidity may account for increased environmental adaptability of *C. tropicalis* or potentially higher levels of exposure from environmental sources (Vogel et al. 2007). Physicians practicing in these regions should be mindful of this epidemiological shift.

C. *tropicalis* BSI is more common (and not infrequently supersedes *C. albicans* BSI) in oncology patients with the highest infection rates seen in bone marrow transplant recipients (11–50%), followed by hematological malignancies (18%) and lowest rates in solid tumors (4–9%) (Viscoli et al. 1999; Alvarez-Gasca et al. 1998; Kontoyiannis et al. 2001; Sipsas et al. 2009; Sabino et al. 2009; Presterl et al. 2007). Investigations of risk factors associated with *C. tropicalis* infection (Abi-Said et al. 1997; Lecciones et al. 1992; Krcmery et al. 1999) have indicated that acute leukemia, neutropenia, and anti-neoplastic therapy are important predisposing factors.

Candidemic episodes involving *C. tropicalis* arising from neonatal intensive care units also occur, but are infrequent compared with *C. albicans* and *C. parapsilosis* (Roilides et al. 2003; Fridkin et al. 2006). Candidal colonization of skin, mucosal or catheter surfaces constitutes the origin of invasive disease, risks of which are increased in very-low birth weight (VLBW) infants < 1500 gram with an immature innate defense system (Singhi et al. 2008; Celebi et al. 2008).

Pathogenesis

C. tropicalis appears to be at least as virulent and pathogenic as any other member of the genus (Wingard 1995; Abi-Said et al. 1997; Nucci et al. 2007). Studies have noted that after colonization, *C. tropicalis* has the ability to rapidly disseminate in the immunocompromised host and cause high mortality. *C. tropicalis* has been reported to cause increased overall crude mortality as compared to other *Candida* spp. (Costa et al. 2000; Pfaller 1996) though other recent studies have not corroborated this trend (Weinberger et al. 2005; Almirante et al. 2005; Sipsas et al. 2009).

Extensive animal studies in the 1930s clearly demonstrated that *C. tropicalis* was pathogenic for mice and rats following inoculation of large microbial doses (Stovall et al. 1933). Studies that followed confirmed the high comparative pathogenicity of *C. tropicalis* to *C. albicans* (Hasenclever et al. 1961). In studies of non-immunocompromised mice, 60–70% of *C. tropicalis* isolates were pathogenic and caused lethal infections within 28 days (Bistoni et al. 1984). Inoculation of *Candida* in murine models produced large differences in the 50% infective dose with *C. tropicalis* notably being more pathogenic than paired strains of *C. albicans*; mirroring clinical observations in the patient groups from which these isolates were collected. In immunocompromised mice *C. tropicalis* has the ability to invade gastrointestinal tract mucosa and disseminate within 30 minutes of inoculation (de-Repentigny et al. 1992). Consequently in these studies 20% of mice infected with *C. tropicalis* died in

comparison to just 4% of those infected with *C. albicans* (Fromtling et al. 1987). In head-to-head studies of virulence of 8 species of *C. albicans* and *C. tropicalis*, the latter were the most pathogenic (Arendrup et al. 2002). These *in-vivo* models provide the experimental evidence showing that *C. tropicalis* is at least as virulent as *C. albicans*, and possibly more virulent than other non-*albicans* species.

Virulence factors

Candida spp. have many virulence attributes which assist in invasion of host tissues. These include adherence to host tissues, production of extracellular enzymes, particularly proteases, the formation of hyphae to aid in evasion of host immune defenses and biofilm production. Pathogenesis of candidiasis has been associated with the differential and temporal regulation of the expression of genes involved in dimorphism, adherence, invasion, and coding for secreted hydrolases (Staib et al. 2001). The secreted enzymes which are considered integral to the pathogenesis of *Candida* are categorized into two main types: proteinases (Hube et al. 1998) which hydrolyze peptide bonds, and phospholipases (Oksuz et al. 2007), which hydrolyze phospholipids. These secreted enzymes facilitate the penetration into the host and counteract the defense system.

Secreted aspartic proteases (SAP) have been intensively investigated in *C. albicans* in which there appear to be at least 10 distinct SAPs. It has been established that different SAPs are important in the ability of the yeast to adhere to mucosa, deep tissue and invade into deep organs (Schaller et al. 1999; De-Bernardis et al. 1999). *C. tropicalis* has been shown to secrete a family of SAP enzymes (SAPt) in invasive disease (Borg-von-Zepelin et al. 1999; Parra-Ortega et al. 2009) demonstrated using reverse transcriptase PCR of RNA isolated from cells grown *in vitro* (Zaugg et al. 2001). SAP activity is important for the adherence of *C. tropicalis* to target cells (Kontoyiannis et al. 2001) and a strain deficient in SAP secretion was less adherent than other protease secreting strains. Whereas the various SAP proteins may digest specific proteins, agglutinin-like sequence (ALS) genes encode cell-surface glycoproteins implicated in adhesion to host surfaces and this have also been identified in *C. tropicalis* (Hoyer et al. 2001). Phospholipases play an active role in the invasion of host tissues by disrupting the epithelial cell membranes and allowing the hyphal tip to enter the cytoplasm (Oksuz et al. 2007).

Biofilm formation

There are multiple factors which predispose individuals to disseminated yeast infections but the implantation of central venous catheters (CVC) appear to be the most common risk factor for the development of disease in patients without neutropenia or major immunodeficiencies (Rex 1996; Tumbarello et al. 2007). Biofilm formation is recognized as a potential virulence factor for the development of candidiasis (d'Enfert 2009). Remarkably, 70–90% of bloodstream isolates of *C. tropicalis* were shown to produce biofilms (Shin et al. 2002; Tumbarello et al. 2007) which was the highest proportion of all *Candida* spp. examined (for other species <25% of blood stream isolates produce biofilms). In addition a clear relationship was demonstrated between the ability of isolates to form biofilms, their isolation from patients with indwelling CVCs and parenteral nutrition. Biofilm formation of silicone rubber voice prosthesis limits the lifetime of the implants causing increased air resistance and valve failure. Combination bacterial and yeast biofilms are commonly isolated from failed prosthetic units with *C. tropicalis* particularly associated with units removed from patients requiring frequent changes (Elving et al. 2002; Elving et al. 2003). Biofilm formation is important in the colonization by *C. tropicalis* of dentures (Dorko et al. 2001) as well as a variety of other plastic devices (catheters, cannulas, and drains) (Dorko et al. 1999) all of which are potential foci of infection. *C. tropicalis* biofilms also demonstrate increased resistance to antifungal agents (Bizerra et al. 2008; Melo et al. 2007). Thus the ability to develop biofilms is a major virulence factor for *C. tropicalis* for certain types of infection.

Spectrum of human disease

Superficial and Localized Mucosal Infections

Superficial infections caused by *C. tropicalis* are rarely reported with isolated cases of subcutaneous abscesses (Benson et al. 1987) and skin and nail infections (Jautova et al. 2001; Kwok et al. 1998). *C. tropicalis* has been reported as part of the normal commensal flora of skin and nails in approximately 10% of patients (Kam et al. 2002). It is the second most common yeast associated with nappy rash (diaper rash) and is isolated in approximately 7% of cases (Dorko et al. 2003).

Carriage of *C. tropicalis* in the normal oral cavity is common with rates approaching 16% (Martin et al. 1983; Luque et al. 2009). Increases in this rate are seen in individuals with dentures (Vanden et al. 2008), HIV infection (Tumbarello et al. 1996; Costa et al. 2006), and irradiation for malignancies (Leung et al. 2000; Thaweboon et al. 2008). Oral thrush and oropharyngeal candidiasis caused by *C. tropicalis* is rare but is present in 3–8% of AIDS patients especially those with recurrent disease (Tumbarello et al. 1996). Oral colonization is common in patients with cancer and it is likely that this is a source of infection in patients who subsequently develop

disseminated invasive disease (Redding et al. 1988; Abi-Said et al. 1997) or might be implicated in disease development (Nieminen et al. 2009). *C. tropicalis* can be isolated from gastric aspirates and translocate from the gut to cause sepsis at distant sites (MacFie et al. 1999; Marshall et al. 1993). Gastric and intestinal colonization by *C. tropicalis* is common in normal individuals (up to 30%) and a recognized risk factor for the development of invasive candidiasis (Cole et al. 1996).

Vaginal infections

C. albicans remains accountable for at least 80–90% of all cases of candidal vulvovaginitis (CVV) (Yang et al. 2003; Richter et al. 2005; Holland et al. 2003). *C tropicalis* is implicated in between 1% to more than 10% of CVV cases (Parazzini et al. 2000; Richter et al. 2005) and these may be associated with recurrent disease and cases with failed primary therapy (particularly after self-medication) (Horowitz et al. 1985).

Urinary tract infections

Candiduria may be found in up to 1–2% of asymptomatic individuals (Fisher et al. 1995; Rivett et al. 1986). Yeast infections of the urinary tract usually present as nosocomial infections and rarely occur as community-acquired infections in a structurally normal urinary tract (Lundstrom et al. 2001). The majority of *Candida* urinary infections are caused by *C. albicans* (51.8%) but a small and significant proportion of more than 10% are caused by *C. tropicalis* (Fraser et al. 1992; Sobel et al. 2000). The incidence of *C. tropicalis* candiduria may be variable and may be suggestively higher in locations whereby *C. tropicalis* BSI rates are significant (Chakrabarti et al. 1997; Paul et al. 2004). An increased incidence of candiduria is also seen in patients with diabetes mellitus (Stapleton 2002) and those suffering from leukemia (Rivett et al. 1986).

Invasive and disseminated infections

Early onset of fungaemia, high APACHE (Acute Physiology And Chronic Health Evaluation) II scores, pretreatment with antifungals and delayed initiation of appropriate therapy are indicators of poor prognosis in candidemia.

Mortality associated with *C. tropicalis* fungaemia is high with rates of 40–70% mortality noted (Leung et al. 2002; Tortorano et al. 2002; Yap et al. 2009). A variety of other specific risk factors have been identified both for the development of the infection and subsequent mortality: these include leukemia, anti-neoplastic chemotherapy, previous neutropenia, central venous catheters, a long stay on intensive care and total parenteral nutrition (Wingard 1995; Abi-Said et al. 1997; Fraser et al. 1992; Leung et al. 2002; Kontoyiannis et al. 2001; Gottfredsson et al. 2003), similar to those predisposing to *Candida* BSI in general. The proportion of infections in children is lower than in adults (MacDonald et al. 1998; Huttova et al. 1998) but is relatively common in pediatric leukemia (Flynn et al. 1993). Leukemia and secondary neutropenia are reportedly independent factors favoring *C. tropicalis* fungaemia (Vigouroux et al. 2006). Sixty to 80% of neutropenic patients colonized with *C. tropicalis* may eventually develop invasive infection (Wingard 1995). Duration of ITU stay tends to be longer in patients with *C. tropicalis* BSI compared to *C. albicans* during the course of infection. Delayed clearance of positive blood cultures may also be encountered in *C. tropicalis* fungaemia. Disease presentation can either be as a disseminated disease similar to other candidaemias or more clinically overt disease with widespread rash and myositis.

C. tropicalis has also been associated with infections in single organs in which the initial infection was almost certainly spread by hematogenous seeding. About 20% of cases of *Candida*-associated vertebral osteomyelitis are due to *C. tropicalis* (Miller et al. 2001). Cases of spondylodiscitis and osteomyelitis (Sebastiani et al. 2001; McCullers et al. 1998), prostatitis (Bastide et al. 2005), pericarditis (Gronemeyer et al. 1982), endocarditis (Zedtwitz-Liebenstein et al. 2001; Nagaraja et al. 2005), and meningitis (McCullers et al. 2000; Flynn et al. 1993) caused by *C. tropicalis* have also been reported.

Endophthalmitis secondary to disseminated candidemia deserves special mention: the eye was thought to be a common end organ target perhaps due to an unusual tropism of *Candida* spp. for the eye as compared to other deep organs (Klotz et al. 1992; Sallam et al. 2006). Affected patients may notice a decreased in visual acuity. The incidence of endogenous *Candida* endophthalmitis was historically estimated to be 28–45% of hospitalized patients with candidemia (Parke et al. 1982). More recently stricter criteria for diagnosis and early treatment of candidemic patients with antifungal agents have brought the incidence down; now estimated to be 1–3% (Rodriguez-Adrian et al. 2003). Limited case series of endopthalmitis attributable to *C. tropicalis* had a reported incidence of 2–45% in fungemic patients (Feman et al. 2002) but predisposition to endophthalmitis by any particular *Candida* species is not thought to have increased.

Chronic disseminated candidiasis (CDC) represents a distinct form of disseminated *Candida* infection with predominant involvement of the liver, spleen and occasionally kidney (Figure 5). This entity occurs in the setting of leukemic patients with neutropenia from chemotherapy.

Though this specific immunocompromised group of patients is particularly associated with predisposition to *C. tropicalis* as discussed above, the predominant *Candida* species implicated in CDC patients seems proportional to the local *Candida* BSI epidemiology as per institution/country (Chen et al. 2003; Masood et al. 2005).

Dermatological manifestations of disseminated candidiasis caused by *C. tropicalis* occur with symptoms varying from papular nodular eruptions to necrotic skin lesions (Fraser et al. 1992; Wolfson et al. 1985) in most cases it is possible reach a diagnosis by histology and culture of the lesion (Figure 6).

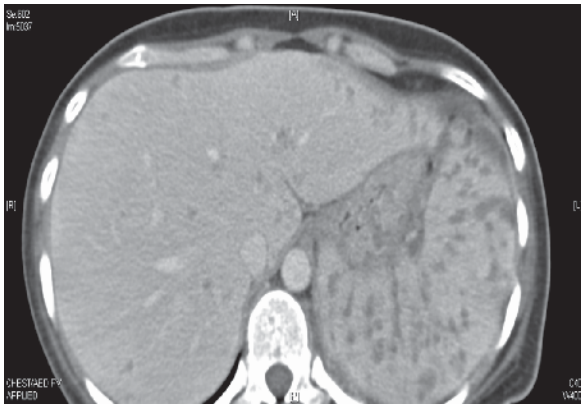

Figure 5. Chronic disseminated candidiasis with multiple hypodense lesions in liver and spleen.

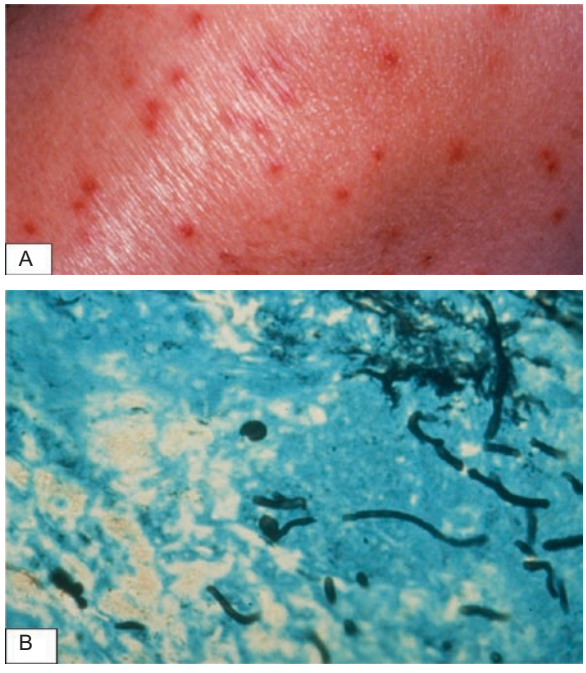

Figure 6. (A) Cutaneous papular eruptions in patient with disseminated candidemia. (B) Biopsy of skin lesion showing yeast cells and numerous pseuohyphae in tissue. GMS stain x250.

C. tropicalis *and nosocomial infection*

It has been suggested that there is a potential for cross-transmission of *C. tropicalis* between health-care workers and patients. In experimental studies with human volunteers it was demonstrated that *C. tropicalis* was able to survive on the hands and inanimate surfaces for up to 24 hours. Transmission was also demonstrated from one hand to a second (69%) and a second hand to a third (38%) (Rangel-Frausto et al. 1994). Nosocomial clustering of *C. tropicalis* candidemia have been documented by genotyping (Chai et al. 2007; Asmundsdottir et al. 2008). Nosocomial *C. tropicalis* candiduria within an intensive care unit had also been attributed epidemiologically to environmental contamination from improper disposal of medical waste (Jang et al. 2005). Within neonatal/pediatric intensive care units, outbreaks of *C. tropicalis* bloodstream infections have been a cause for concern (Roilides et al. 2003;Roilides et al. 2004; Chowdhary et al. 2003). The tightening of infection control practices in some cases contained the outbreaks. These data clearly suggest the potential for transmission of *C. tropicalis* within the hospital environment.

Molecular epidemiology

Strain identification and genetic diversity are vital for understanding the epidemiologic aspects of nosocomial *Candidal* infection (Kleinegger et al. 1996), acquisition and nosocomial transmission (Burnie et al. 1985). Strain categorization may help in evaluating mechanisms of infection, whether re-infection or relapse and the development of antifungal resistance (Espinel-Ingroff et al. 1996; Pfaller et al. 1994).

PCR-based typing methodologies for *C. tropicalis* are available. For instance random amplified polymorphic DNA (RAPD) (Steffan et al. 1997; Lin et al. 1995) has been used in many studies but reproducibility (both between and within laboratories) is lacking. Variations in the banding pattern generated have been caused by a multitude of factors including primer-to-template concentration and replication conditions. Pulsed-field gel electrophoresis (PFGE) allows typing of *C. tropicalis* by electrophoretic karyotyping (Espinel-Ingroff et al. 1996; Doebbeling et al. 1993). However many of the chromosomes of *C. tropicalis* are of similar size and appear as a large complex band (Espinel-Ingroff et al. 1999) with poor resolution. PFGE typing can be improved if DNA is treated with certain cutting restriction endonucleases: Espinel-Ingroff et al. (Espinel-Ingroff et al. 1999) used *C. tropicalis* DNA treated with either *Sfi* I or *Bss*HII endonucleases before PFGE. The fingerprints were reproducible and discriminatory between strains. RFLP-PFGE is a reliable tool to study

strain-to-strain variations in epidemiologic evaluations of *C. tropicalis*.

Multi-locus sequence typing (MLST), a technique in which the sequences of housekeeping gene fragments are compared is now available for *C. tropicalis*. using genes ICL1, MDR1, SAPT2, SAPT4, XYR1, and ZWF1a. (Chou et al. 2007) Following sequencing, data may be submitted using mlstdbNet software (http://pubmlst.org/ ctropicalis/) to assist in typing and defining the global epidemiology of *C. tropicalis*. This scheme demonstrated that *C. tropicalis* isolates can be grouped into clades based on diploid sequence types (DST). Diversity of the DSTs is greater than was encountered in *C. albicans* and *C. glabrata*.

Antifungal susceptibility testing

Currently the methodology most widely used as a reference standard is based on the Clinical and Laboratory Standards Institute (CLSI) [ex-National Committee on Clinical Laboratory Standards] document M27-A3 on broth dilution antifungal susceptibility testing of yeasts. This is complemented more recently by the European Committee for Standardisation of Antibiotic Susceptibility Testing (AFST-EUCAST) (Cuenca-Estrella et al. 2003) in its reference document. These procedures are intended to provide high levels of standardization and reproducibility in antifungal susceptibility testing but there remain limitations. These include the trailing growth phenomenon, unreliable detection of amphotericin B resistance, and subjective determination of endpoints (Cuenca-Estrella et al. 2002). *C. tropicalis*, in particular, exhibits the lack of a clear endpoint in microwell MIC determination (the presence of a trailing endpoint phenomenon) which occurs in 30–59% of isolates (Arthington-Skaggs et al. 2002). *C. tropicalis* exhibits a relatively lower level of agreement between the CLSI and EUCAST procedures amongst the *Candida* species. Reduction in the incubation period from 48 to 24 hours incubation does reduce the trailing growth phenomenon but there are concerns about accuracy at 24 hours using CLSI guidelines (Espinel-Ingroff et al. 2009). *In vivo* studies in murine models of disseminated candidiasis have shown that isolates exhibiting trailing endpoints with azoles should be regarded as susceptible rather than resistant (Warn et al. 2000). This is supported by clinical studies of oropharyngeal candidiasis due to strains with trailing growth responding to low dose fluconazole (similar to those used to treat typical strains) (Revankar et al. 1998).

Agar-based disk diffusion method and E-test are alternatives to the reference methods of susceptibility testing of yeasts including *C. tropicalis* (Chryssanthou 2001; Alexander et al. 2007). These procedures are relatively straightforward and offer a practical alternative for the busy hospital laboratory. Overall agreement with the reference methods for *Candida species* is in excess of 80% with fluconazole (Chryssanthou et al. 2002; Simor et al. 1997).

Breakpoints

Breakpoints established by the CLSI for some of the antifungal agents in common use are shown in Table 1. In contrast to the CLSI guidelines, the latest clinical breakpoint for fluconazole as defined by EUCAST for *Candida* species including *C. tropicalis* (with the exception of C. *glabrata* and C. *krusei*) has been set at ≤2mg/L for susceptible strains with resistance at >4mg/L without the susceptible-dose dependent intermediate range as per CLSI (2008).

Fluconazole

C. tropicalis was for a long time regarded as a species largely susceptible to fluconazole and amphotericin B (>95–98%) but reports over the last ten years have shown development of resistance to fluconazole in some centers and clinical failure (*in-vivo* resistance) (Abi-Said et al. 1997; Antoniadou et al. 2003). In virtually every instance in which resistant *C. tropicalis* has occurred the patient has been on fluconazole treatment (Law et al. 1994; Leroy et al. 2009) and therefore assumed that resistant strains probably do not spontaneously occur without drug pressure (Rex et al. 1995b). Development of resistance to fluconazole is particularly seen in AIDS, intensive care and leukemia patients (Law et al. 1994) but is rare in other cases. *In-vitro* resistance to fluconazole has been associated with a worse prognosis and increased mortality (Law et al. 1994; Rex et al. 1995b; Bille et al. 1997). The reason for this rapid increase in resistance is unknown but a variety of mechanisms of resistance have been identified from individual isolates.

The susceptibility of more than 1,000 *C. tropicalis* isolates to fluconazole as determined by CLSI (S) MIC ≤ 8 μg/ml (broth microdilution method) is ≥ 98% in an international surveillance program (Pfaller et al. 2006), though the MIC_{90} (overall MIC at which 90% of isolates are inhibited) is higher in *C. tropicalis* (2 μg/ml) than *C. albicans* (0.5 μg/ml). Absolute resistance to fluconazole,

Table 1. Breakpoints established by CLSI for some of the antifungal agents in common use (all values in mg/L) against *Candida* spp.

	Susceptible	Susceptible-dose dependent	Resistant
Fluconazole	≤8.0	16-32	≥64
Itraconazole	≤0.125	0.25-0.5	≥1
Flucytosine	≤4.0	8-16	≥32
Amphotericin B	None given	None given	None given
Ketoconazole	None given	None given	None given

designated as MIC ≥64 μg/ml, has remained infrequent at ≤3% worldwide for *C. tropicalis.* Nonetheless, it is notable that a recent Asian national anti-fungal surveillance program reported an increasing rate of reduced susceptibility to fluconazole in *C. tropicalis* isolates exhibiting the trailing phenomenon (Yang et al. 2008).

Limited specific information is available about the molecular mechanisms of resistance to azoles in *C. tropicalis* but the mechanisms are likely to be similar to those identified in other *Candida* species. Two major mechanisms of azole resistance are generally recognized: one involves mutations in the gene (ERG11) encoding 14-α-demethylase, a target enzyme; and the second involving multidrug efflux transporters encoded by MDR/CDR genes (Casalinuovo et al. 2004). There has been a single report identifying overexpression of CtERG11 and a missense mutation in this gene being responsible for acquired azole resistance in *C. tropicalis* (Vandeputte et al. 2005). A recently described efflux pump inhibitor MC-510,027 which specifically inhibits the activity of the MDR pumps (encoded by CDR genes) has also been shown to reverse *C. tropicalis* resistance to both fluconazole and itraconazole (Wise 2001), reducing the MIC to fluconazole from >128 to 1 μg/ml and itraconazole from >8 to 0.008 μg/ml. Experimentally induced fluconazole resistance has been generated in *C. tropicalis* (Barchiesi et al. 2000) with a single sub-culture in azole-containing medium. The strains were cross-resistant to itraconazole and terbinafine but gradually lost their resistant phenotype on serial passage in drug free medium. The azole-resistant isolates revealed upregulation of the two different multidrug efflux transporter genes: the major facilitator gene *MDR1* and the ATP-binding cassette transporter gene *CDR1*.

Itraconazole

Itraconazole is also active against most isolates of *C. tropicalis* but with MICs ten times lower than fluconazole. High level resistance in *C. tropicalis* to itraconazole is rare but strains with reduced susceptibility to fluconazole require higher inhibitory concentrations of itraconazole due to cross resistance and therefore patients will require higher doses for treatment, with possible sub-optimal response to itraconazole (Johnson et al. 1995; Barchiesi et al. 1994). Recent studies have demonstrated that parallel increases in both itraconazole and fluconazole MICs can be correlated to increases in multidrug efflux transporters (CtMDR1 and CDR1) (Barchiesi et al. 2000).

Extended-spectrum triazoles

Voriconazole is highly active against *C. tropicalis*; for susceptible strains it was significantly more potent than itraconazole and ketoconazole with MICs up to 10 times lower (Dannaoui et al. 2009). As seen with itraconazole and ketoconazole, strains with higher fluconazole MICs also tend to have much higher voriconazole MICs suggesting cross-resistance which probably results from similar mechanisms of action of these agents (Nguyen et al. 1998; Barchiesi et al. 1994). Posaconazole is also highly active against *C. tropicalis* with MICs approximately equivalent to itraconazole and nearly ten times lower than fluconazole (Pfaller et al. 1997; Laverdiere et al. 2002). It is also an option in HIV-infected subjects with azole-refractory oropharyngeal and oesophageal candidiasis (Skiest et al. 2007). Nonetheless, it is most efficacious as a potent broad spectrum triazole reserved for life-threatening fungal infections refractory to first line therapies (Torres et al. 2005). As seen with itraconazole, ketoconazole and voriconazole strains with raised MICs to fluconazole also appear to be less susceptible to posaconazole (Pfaller et al. 1997). This high-level azole cross-resistance has only been seen with *C. albicans* and *C. tropicalis*. Ravuconazole and isavuconazole has similar high activity against *C. tropicalis*, MICs being about a fifth those of itraconazole (approximately the same level of activity as voriconazole) (Laverdiere et al. 2002; Majithiya et al. 2009).

Amphotericin B

Amphotericin B had been the mainstay of antifungal therapy for many years. It has a relatively broad spectrum of action: resistance (MIC > 2μg/ml) is rare and tends to be species-specific (Ellis 2002). Nonetheless, intolerance of amphotericin B deoxycholate infusion and nephrotoxicity are well described (Pfaller et al. 2007a; Herbrecht et al. 2002). Lipid-associated formulations are available with fewer side effects. Resistance of *C. tropicalis* to amphotericin B is rare and few strains have reliably demonstrated high-level resistance to this agent (Rex et al. 1995a; Warn et al. 2002).

Flucytosine (5FC)

Currently approximately 5% of naïve *C. tropicalis* isolates are resistant to 5FC. Resistance had been reported to develop rapidly during therapy with up to 58% of strains resistant in some centers (Fleck et al. 2007). 5FC should be preferably be used in combination therapy with other antifungals and not as a single agent.

Echinocandins

The echinocandins are non-competitive inhibitors of cell wall (1-3)-ß-D-glucan synthase complex. There are three echinocandin agents in clinical use – caspofungin, micafungin, and anidulafungin. The mechanism of activity of the echinocandins against *Candida* is predominantly

fungicidal.(Espinel-Ingroff 1998) Due to this different mode of action, cross-resistance with triazoles and the polyenes is unlikely (Pfaller et al. 2003). Caspofungin has demonstrated good efficacy against oropharyngeal and oesophageal candidiasis in adults (Arathoon et al. 2002) and also demonstrated good activity against invasive candidiasis (Zaas et al. 2006). *In vitro* susceptibilities demonstrate low MICs in the range 0.03-0.5 μg/ml (Roling et al. 2002). Recently though, a caspofungin-resistant strain of *C. tropicalis* has been reported (Pasquale et al. 2008). Micafungin has demonstrated efficacy comparable to amphotericin B and little toxicity (Kuse et al. 2007). *In vitro* susceptibilities demonstrate micafungin MICs for *C. tropicalis* 10 times lower than caspofungin (Mikamo et al. 2000). Anidulafungin demonstrates similar efficacy to caspofungin and micafungin (MIC range 0.015–0.5 μg/ml).(de la et al. 2007) Clinical response of *C. tropicalis* infections to anidulafungin was significantly better than that to fluconazole in a recent randomized study ($p = 0.04$) (Torre et. al. 2007). Aminocandin is a new member of the echinocandins that is currently in phase I/II development that has demonstrated excellent *in vivo* activity in murine models of fluconazole-resistant *C. tropicalis* (Warn et al. 2005).

Summary on treatment of *C. tropicalis* candidiasis

Numerous consensus guidelines for the treatment of candidiasis are available. None distinguish the treatment of *C. tropicalis* infections from other *Candida* species (Slavin et al. 2004; Denning et al. 2003; Pappas et al. 2004; Pappas et al. 2009). Until recently, most studies did not report the outcomes by individual species of *Candida*. In Table 2 we have tabulated those that are available in major trials involving invasive candidiasis; and as illustrated, due to the localities where some of these trials were conducted, *C. tropicalis* candidemia may constitute less than 10% of the cases enrolled and the reader will need to be mindful interpreting outcomes of such occasional under-sized cohorts. Differences in response rates between these trials are as dictated by the individual trial protocols. Generally, *C. tropicalis* follows a similar response to the respective therapeutic interventions as *C. albicans* with the statistical design of these trials intended as non-inferiority studies. Satisfactory therapeutic responses have been demonstrated with amphotericin B, fluconazole (intravenous/oral), extended spectrum triazoles and the echinocandins. An exception worth mentioning though is the voriconazole versus amphotericin/fluconazole trial (Kullberg et al. 2005) in which saw a much higher response rate of *C. tropicalis* in the voriconazole treatment group (32%) than the amphotercin/fluconazole group (6%) though the infecting strains were susceptible to all trial drugs. The authors were unable to account for this disparity beyond attributing this to the small sample size. The recent IDSA update of 2009 (Pappas et al. 2009) highlights the prevention of invasive candidiasis in high-risk neonates and adults and provides guidelines on the empiric treatment of suspected invasive candidiasis in adults.

Over the last 3 years, sufficient data has been generated from large randomized controlled trials to make tentative conclusions about the treatment of invasive *C. tropicalis* infections, including candidemia. Treatment options for *C. tropicalis* invasive candidiasis are as summarized in Table 3. Amphotericin B preparations or an echinocandin are effective treatments for primary *C. tropicalis* candidiasis. Likewise voriconazole is also effective therapy, but has other limitations in acutely ill patients. Liposomal amphotericin is substantially less toxic than deoxycholate amphotericin B. There appears to be no difference in outcome in *C. tropicalis* infections between the 3 licensed echinocandins, and the doses studied in the randomized controlled studies appear sufficient for good results (Table 2).

Removal or change of appropriate intravascular catheter remains an integral component of candidemia treatment which should not be overlooked. Ophthalmic assessment for endophthalmitis is also recommended. Vitrectomy with topical intra-vitreal antifungal administration needs to be considered in *Candida* endophthalmitis on top of systemic antifungal treatment. Repeat blood cultures to document clearance of *C. tropicalis* fungemia is also advisable. Once the patient is stable, and has responded, and the susceptibility of the isolate to fluconazole confirmed, a switch to fluconazole may be made. Duration of therapy should last for 14 days after the last negative culture accompanied by clinical improvement.

Conclusions

C. tropicalis accounts for a significant proportion of *Candida* bloodstream isolates in tropical regions and is implicated much more frequently in infections of cancer patients. Mortality associated with *C. tropicalis* fungaemia can be high though this may inherently be attributable to the more severely ill patient cohort at-risk. Naïve *C. tropicalis* appear to be susceptible to a wide range of antifungal agents and intrinsic resistance is rare or absent. The development of resistance to fluconazole often causes cross-resistance to the whole triazole group of antifungal drugs (including the new broad-spectrum triazoles).

Early diagnosis and prompt initiation of appropriate antifungal therapy will hopefully help to reduce the morbidity and mortality associated with *C. tropicalis* infections.

Table 2. Randomised trials of candidaemia/invasive candidiasis (IC) and response of *Candida tropicalis* as per individual trial protocol.

			Response of *Candida tropicalis* to treatment						
					Flucon &		Echinocandins		
Study	Design	Trial Conclusion for Candidaemia/IC	Flucon	Am B	AmB	Vori	Caspo	Mica	Anidula
Rex 1994 (NEJM 331:1325-30)	AmB 0.5–0.6 mg/kg/day vs Flu 400 mg/day	Fluconazole and AmB not significantly different in treating candidaemia in non-neutropenic patients	14/18 (78%)	12/13 (92%)	n.a.	n.a.	n.a.	n.a.	n.a.
Rex 2003 (Clin Infect Dis 2003;36:1221-8)	Flu 800 mg vs Flu 800 + AmB 0.7 mg/kg/day	Combination therapy not antagonistic in non-neutropenic patients with candidaemia; trend towards improved success with combination	4/7 (57%)	n.a.	10/13 (77%)	n.a.	n.a.	n.a.	n.a.
Mora-Duarte, 2002 (NEJM 347:2020-9)	Caspofungin 70 mg (1st day) then 50 mg daily vs AmB 0.6-1.0 mg/kg/day	Caspofungin as effective as AmB for candidaemia/invasive candidiasis	n.a.	10/14 (71%)	n.a.	n.a.	17/20 (85%)	n.a.	n.a.
Kullberg, 2005 (Lancet 366:1435-42)	Voriconazole 12mg/kg/day × 24hrs then 6 mg/kg/day vs AmB 0.7–1.0 mg/kg/day followed by fluconazole 400 mg/day	Both regimens are as effective in treatment of candidaemia in non-neutropenic patients	n.a.	n.a.	1/16 (6%)	17/53 (32%)	n.a.	n.a.	n.a.
Kuse, 2007 (Lancet 369:1519-27)	Micafungin 100 mg/day vs liposomal AmB 3 mg/kg/day	Micafungin as effective as liposomal AmB in candidaemia	n.a.	50/75 (67%)[a]	n.a.	n.a.	n.a.	54/76 (71%)	n.a.
Reboli, 2007 (NEJM 356:2472-82)	Anidulafungin 200 mg (1st day) then 100 mg daily vs fluconazole 800 mg (1st day) then 400 mg daily	Anidulafungin non-inferior to fluconazole in invasive candidiasis	4/8 (50%)	n.a.	n.a.	n.a.	n.a.	n.a.	13/14 (93%)
Pappas, 2007 (Clin Infect Dis 45:889-93)	Micafungin (100 mg or 150 mg/day) vs Caspofungin (70 mg on 1st day then 50 mg/day)	Micafungin non-inferior to caspofungin in candidaemia/ invasive candidiasis	n.a.	n.a.	n.a.	n.a.	24/32 (75%)	Mica 100mg daily 21/31 (68%) Mica 150 mg daily 20/33 (61%)	n.a.

[a] = liposomal amphotericin B; n.a. = not available.

Table 3. Summary on treatment of primary invasive *C. tropicalis*.

First line Treatment	Dose	Comments
Amphotericin B deoxycholate	0.7–1mg/kg /day	Equivalent lipid-associated formulations are suitable alternatives
Caspofungin	70mg loading dose then 50mg/day	Intravenous only
Micafungin	100mg/day	Intravenous only
Anidulafungin	200mg loading dose then 100mg/day	Intravenous only
Alternative treatments		
Voriconazole	6mg/kg loading dose twice then 3mg/kg 12 hourly	Intravenous or oral preparations available
Voriconazole	200mg BD oral	Oral alternative if strain is fluconazole resistant (ensure strain is susceptible *in vitro* to voriconazole as cross resistance occurs)

Option to switch to fluconazole 400–800 mg/day (oral or intravenous) when patient's condition stabilises and microbiological susceptibility testing indicates sensitivity to fluconazole.
Treatment duration
14–21days after last positive blood culture with clinical resolution in candidaemia.
3–6 months with clinical and radiological resolution in chronic disseminated candidiasis.
In neutropenic/immunocompromised patients, higher dose range and longer duration therapy to be considered, with low threshold for utilization of alternative agents where appropriate; or when other concurrent fungal pathogens suspected.

Acknowledgements

We are grateful to David Fitzpatrick for permission to use Figure 1.

L.C. was supported by the Health Manpower Development Plan (HMDP) Fellowship, Ministry of Health, Singapore and the International Fellowship, Agency for Science, Technology and Research (A*STAR)/National Medical Research Council (NMRC), Singapore.

PAW is funded by the Fungal Research Trust, Macclesfield UK.

Declaration of interest

PAW has received grant support from Basilea and The Medical Research Council, The Fungal Research Trust and the National Institute of Allergy and Infectious Diseases. He has been an advisor/consultant to F2G, Basilea and Nektar and is a Director and holds shares in Euprotec Ltd. In the past 5 years, DWD has received grant support from Astellas, Merck, Pfizer, F2G, AstraZeneca, Indevus, Basilea, The Fungal Research Trust, The Wellcome Trust, The Moulton Trust, The Medical Research Council, The Chronic Granulomatous Disease Research Trust, National Institute of Allergy and Infectious Diseases, National Institute of Health Research, and the European Union; he has been an advisor/consultant to Basilea, Vicuron (now Pfizer), Pfizer, Schering Plough, Indevus, F2G, Nektar, Daiichi, Sigma Tau, Astellas, Gilead, and York Pharma; he has been paid for talks on behalf of Schering, Astellas, Merck, and Pfizer and holds founder shares in F2G Ltd. and Myconostica Ltd., both University of Manchester spin-out companies. CL declares no conflicts of interest.

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