mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Review article

Diagnosis and therapy of *Candida* infections: joint recommendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy

Markus Ruhnke,[1] Volker Rickerts,[2] Oliver A. Cornely,[3] Dieter Buchheidt,[4] Andreas Glöckner,[5] Werner Heinz,[6] Rainer Höhl,[7] Regine Horré,[8] Meinolf Karthaus,[9] Peter Kujath,[10] Birgit Willinger,[11] Elisabeth Presterl,[12] Peter Rath,[13] Jörg Ritter,[14] Axel Glasmacher,[15] Cornelia Lass-Flörl[16] and Andreas H. Groll[14]

[1]*Medizinische Klinik m. S. Onkologie u. Hämatologie, Charité Universitätsmedizin, Charité, Campus Mitte, Berlin, Germany,* [2]*Medizinische Klinik II, Klinik der Johann Wolfgang Goethe-Universität, Frankfurt a. M., Germany,* [3]*Department I for Internal Medicine, ZKS Köln, and CECAD, University of Cologne, Cologne, Germany,* [4]*Medizinische Klinik III, Universitätsklinikum Mannheim der Universität Heidelberg, Germany,* [5]*Neurologisches Rehabilitationszentrum, BDH-Klinik Greifswald GmbH, Germany,* [6]*Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Germany,* [7]*Klinik für Anästhesiologie und operative Intensivmedizin, Klinikum Nürnberg, Nürnberg, Germany,* [8]*Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany,* [9]*Klinik für Hämatologie und Onkologie, Städtisches Klinikum München GmbH, München, Germany,* [10]*Klinik für Chirurgie, Universitätsklinikum Schleswig- Holstein, Campus Lübeck, Germany,* [11]*Klinische Abteilung für Mikrobiologie, Medizinische Universität Wien, Germany,* [12]*Klinische Abteilung für Infektionen und Tropenmedizin, Medizinische Universität Wien,* [13]*Institut für med. Mikrobiologie, Uniklinikum Essen, Essen, Germany,* [14]*Klinik und Poliklinik für Kinderheilkunde, Pädiatrische Hämatologie/Onkologie, Universitätsklinikum Münster, Germany,* [15]*Medizinische Klinik und Poliklinik III am Univ. Klinikum Bonn, Bonn, Germany and* [16]*Sektion für Hygiene und medizinische Mikrobiologie, Medizinische Universität Innsbruck, Innsbruck, Germany*

Summary

Invasive *Candida* infections are important causes of morbidity and mortality in immunocompromised and hospitalised patients. This article provides the joint recommendations of the German-speaking Mycological Society (Deutschsprachige Mykologische Gesellschaft, DMyKG) and the Paul-Ehrlich-Society for Chemotherapy (PEG) for diagnosis and treatment of invasive and superficial *Candida* infections. The recommendations are based on published results of clinical trials, case-series and expert opinion using the evidence criteria set forth by the Infectious Diseases Society of America (IDSA). Key recommendations are summarised here: The cornerstone of diagnosis remains the detection of the organism by culture with identification of the isolate at the species level; *in vitro* susceptibility testing is mandatory for invasive isolates. Options for initial therapy of candidaemia and other invasive *Candida* infections in non-granulocytopenic patients include fluconazole or one of the three approved echinocandin compounds; liposomal amphotericin B and voriconazole are secondary alternatives because of their less favourable pharmacological properties. In granulocytopenic patients, an echinocandin or liposomal amphotericin B is recommended as initial therapy based on the fungicidal mode of action. Indwelling central venous catheters serve as a main source of infection independent of the pathogenesis of candidaemia in the individual patients and should be removed whenever feasible. Pre-existing immunosuppressive treatment, particularly by glucocorticosteroids, ought to be discontinued, if feasible, or reduced. The duration of treatment for uncomplicated candidaemia is 14 days following the first negative blood culture and resolution of all associated symptoms and findings. Ophthalmoscopy is recommended prior to the discontinuation of antifungal chemotherapy to rule out endophthalmitis or chorioretinitis. Beyond these key recommendations, this article provides detailed recommendations for specific disease entities, for antifungal treatment

Correspondence: Prof. Dr med. Markus Ruhnke, Medizinische Klinik und Poliklinik mit Schwerpunkt Onkologie/Hämatologie, Charité Universitätsmedizin, Charité Campus Mitte, Charitéplatz 1, 10117 Berlin, Germany. Tel.: +49 304 505 13102. Fax: +49 304 505 13907. E-mail: markus.ruhnke@charite.de

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in paediatric patients as well as a comprehensive discussion of epidemiology, clinical presentation and emerging diagnostic options of invasive and superficial *Candida* infections.

Key words: Mycoses, *Candida*, fungal infection, candidaemia, candidosis, candidiasis.

Introduction

Invasive fungal infections caused by yeast of the genus *Candida* are important causes of morbidity in immunocompromised and hospitalised patients. Regional factors have a profound impact on the epidemiology of infections due to *Candida*. Management of patients with invasive *Candida* infection is increasingly challenging for the clinician due to an increase in non-culture based diagnostic techniques that are introduced into clinical practice and the availability of new antifungal treatment options. Therefore, it appears to be important to review current data on the aetiology, epidemiology, diagnosis and treatment of invasive candidosis.

This article includes the joined recommendations of the 'Deutschsprachigen Mykologischen Gesellschaft (DMYKG)' and the 'Paul-Ehrlich-Gesellschaft für Chemotherapie (PEG)' on the diagnosis and treatment of superficial and invasive candidosis. The recommendations were drafted by a joint working group of experts of both societies chaired by the chairmen of the DMYKG and the Antifungal Chemotherapy Section of the PEG using an iterative process based on published clinical trials, case-series and expert opinion. The recommendations are graded using a system suggested by the Infectious Diseases Society of America (IDSA) (see Table 1).[1,2] The strength of the recommendations is ranked from A–C and the quality of the evidence for a recommendation by I–III.

Table 1 Evidence criteria as used by the Infectious Diseases Society of America (IDSA).[1,2]

1. Strength of recommendation
   - A = good evidence to support a recommendation
   - B = moderate evidence to support a recommendation
   - C = poor evidence to support a recommendation
2. Quality of evidence
   - I = evidence from ≥1 properly randomised controlled trial
   - II = evidence from ≥1 well-designed clinical trial, without randomisation; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled experiments
   - III = evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Aetiology

Yeast of the genus *Candida* are frequent colonisers of the skin and mucous membranes of animals and dissemination in nature is widespread. Only a few of the more than 150 described species are regularly found as infectious agents in humans. *Candida albicans* is considered to be the most important pathogen. Others, such as *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida dubliniensis*, *Candida lusitaniae* and *Candida guilliermondii* are increasingly being recognised as causes of *Candida* infections.[3]

Pathogenesis and risk factors

The spectrum of diseases caused by *Candida* consists of superficial and invasive *Candida* infections.

Infections of the mucous membranes are associated with defects in cellular immunity such as the depletion of CD4-positive T-helper cells in patients with HIV-infection, after haematopoietic stem cell transplantation, in patients treated with steroids and antineoplastic agents (e.g. fludarabine), in graft-versus-host disease (GvHD) or after radiation therapy.[4–6] Other predisposing factors include diabetes mellitus, therapy with antibacterial agents or local factors such as the use of a dental prosthesis.[7–9]

Most infections are caused by yeast that colonise the skin or mucous membranes.[10] The oropharynx and the gastrointestinal tract are considered to be the most important portals of entry. In addition, intravenous catheters, which may be colonised through the skin or via the bloodstream, serve as entry for yeast to the bloodstream. In addition, poor hand hygiene of health care professionals is a potential source for nosocomial infections.[7,11–13]

Clinical manifestations include pyrexia, a sepsis-like syndrome, and disseminated infection with microabscesses or infarctions of various organs such as skin,

the kidneys, the myocardium, the liver, the spleen, the bone, the CNS or eyes with retinal lesions and consecutive symptoms due to loss of function of these structures.[14–16] Persistent candidaemia is an important risk factor for disseminated infection/disease, especially in children.[17] Chronic infections may be characterised by small abscesses or a granulomatous reaction in infected tissue that may lead to calcification with only a limited number of vital fungi. Patterns of tissue damage may vary depending on the involved organ (liver, lung and CNS).[18–20]

Risk factors for invasive candidosis include the prolonged use of broad spectrum antibacterial agents, treatment with steroids, central venous catheters, parenteral nutrition, the colonisation of mucous membranes, major abdominal surgery, especially after gut perforation, a prolonged duration of granulocytopenia, acute renal failure, haemodialysis and a birth weight below 1000 g (see Table 2).[21–28]

Invasive candidosis is a serious, potentially lethal disease. Studies from the early 1980s demonstrated mortality rates of up to 70%.[29,30] Recent publications reported an attributable mortality between 15% and 50%.[31–37] Factors associated with mortality are: (1) persistent positive blood cultures, (2) visceral dissemination, (3) persistent granulocytopenia and (4) a delayed start of antifungal therapy.[2,29,38–42]

Epidemiology

There are no recent data on the incidence of oral and oesophageal candidosis. Oropharyngeal candidosis is found in 6% to 93% of HIV-infected patients.[43] The incidence has dramatically decreased since the introduction of highly active antiretroviral therapy (HAART).[44,45] Without antifungal prophylaxis, 25–35% of patients with cancer or after haematopoietic stem cell transplantation develop oropharyngeal candidosis.[39,46,47] Most infections are caused by *C. albicans*, although mixed infections (in combination with *C. glabrata* or *C. dubliniensis*) may be found especially in HIV-infected patients.[48–50]

Candidaemia is most often caused by *C. albicans* (45–65%), followed by *C. glabrata* (15–30%), *C. tropicalis* (10–30%), *C. parapsilosis*, *C. krusei*, *C. lusitaniae* and *C. guilliermondii*. Other species such as *C. dubliniensis*, *Candida rugosa*, *Candida stellatoidea*, *Candida famata*, *Candida norvegensis* and *Candida kefyr* are only rarely recovered from blood cultures. The aetiology of candidaemia may differ between patient groups, different hospitals and geographic regions. While *C. albicans* remains the most important agent among all risk groups, a shift to non-*Candida albicans* yeast is being reported from several hospitals.[51] Especially in patients with haematological malignancies, non-*Candida albicans* yeast (*C. glabrata and C. krusei*) are more frequently found than in patients with solid tumours or in non-granulocytopenic ICU patients.[35,51] *Candida parapsilosis* is more prevalent in the paediatric patient population (especially in association with intravenous catheters) while *C. glabrata* is more often found in older patients.[51–54] In addition, exposure to fluconazole, broad spectrum antibacterial agents and severe underlying diseases are known predispositions for non-*Candida albicans* yeast, especially *C. glabrata*.[54]

Pathogens of the species *Candida* are found in 5% to 15% of all positive blood cultures. The rates differ among different countries, hospitals and wards.[55] Nosocomial candidaemia is diagnosed in 5–10 patients per 10 000 hospital admissions. In acute care hospitals in the US, 4.8 cases of candidaemia were found per 10 000 days with central venous catheters.[56] The incidence of nosocomial candidaemia in adults increases with patient age but is highest among neonatals.[36,57,58] A large survey in the US documented the incidence of candidaemia in neonates with 15 per 10 000 hospital admissions, compared to 4.7 in paediatric patients and 3.0 in adults.[36,58] A European point prevalence study that included all 3147 patients treated for sepsis in intensive care units documented *Candida* spp. in 17% of cases as the aetiological agent.[59,60] In autopsied cancer patients, invasive candidosis is found in 7% up to 30% of patients.[61,62] After intensive chemotherapy for solid tumours, candidaemia is found in 0% to 5%.[51,63–66]

Table 2 Risk factors for nosocomial *Candida* infections.

Immunosuppressive therapy
Treatment with broad spectrum antibiotics ≥2 weeks[1]
Centralvenous- or arterial catheters[1]
Parenteral nutrition
Mechanical ventilation ≥10 days
Colonisation with *Candida* at ≥2 regions[1]
Haemodialysis[1]
Relapsed gastrointestinal perforation with secondary or tertiary peritonitis, surgical intervention in patients with acute pancreatitis[1]
Severe illness as measured by 'morbidity score' (APACHE II/III >20)
Acute renal failure[1]
Granulocytopenia
Acute and chronic graft-versus-host disease (GvHD) following allogeneic stemcell transplantation (HSCT)
Intensive care unit for ≥9 days
Polytransfusions
Preterm neonates (≤1000 g)

[1]'Independent' risk factors.[21–25]

Epidemiological trends may differ between European countries. Whereas the incidence and species distribution in Switzerland did not change between 1991 and 2000, an increasing incidence has been described in Scandinavian countries (from 1.7 to 2.2 cases per 100 000 inhabitants in Finland and from 6.5 to 15.6 cases in Norway) without a shift in the relative amount of different *Candida* species.[67–71] A shift in the aetiology of candidaemia has been documented in Slowakia and France, where the rate of non-*Candida albicans* yeast, especially *C. glabrata* increased in 10 years from 0% to 46%.[72,73] By contrast, in Spain and Italy, *C. parapsilosis* is the predominant agent of candidaemia after *C. albicans*.[74,75] A study in Denmark documented an increase in the incidence of candidaemia from 2003 to 2004 with *C. glabrata* being second after *C. albicans*. The rate of *C. glabrata* varied between 8% and 32% in different hospitals.[76] A study in the UK also found *C. albicans* (64.7%) and *C. glabrata* (16.2%) as the most important agents with the highest incidence of *C. glabrata* described in surgical patients.[77] The aetiology in Germany is comparable with the data from the UK and Denmark (*C. albicans* 58.5%, *C. glabrata* 19.1%, *C. parapsilosis* 8.0%, *C. tropicalis* 7.5%).[78,79]

Fungaemia due to non-*Candida* yeast (e.g. *Trichosporon* spp., *Blastoschizomyces* (*Geotrichum*) *capitatum*, *Rhodotorula rubra* or *Saccharomyces cerevisiae*) are reported infrequently. However, the correct identification requires additional laboratory tests that are not available in all laboratories.[80–85] These yeast are often characterised by a reduced *in vitro* activity of antifungal agents.[86,87] The diagnosis of mixed infections is important as this may have therapeutic consequences.[85,88]

Clinical manifestations

Several clinical entities of invasive candidosis have been distinguished by Bodey *et al.* This scheme is mainly used in the US and English-speaking countries[89]:

- Isolated candidaemia (with, or without intravenous catheter);
- Acute disseminated candidosis with/without fungaemia and disseminated organ involvement;
- Invasive candidosis restricted to only one organ (e.g. endocarditis, meningoencephalitis, peritonitis);
- Chronic disseminated candidosis in patients with haematological malignancy.

Superficial candidosis may be subdivided in infections of the skin and the mucous membranes such as oral and vulvovaginal candidosis. Oral candidosis is characterised by white, adherent, painless discrete or confluent patches, may be associated by angular cheilitis and dysgeusia and can impair oral food intake.[90] In the HIV-infected patient, oral candidosis is typically seen in advanced immunodeficiency.[91–94] In the absence of distinct patches, diagnosis of oral candidosis may be impaired when only inflamed and dry, atrophic oral mucosa is present.[91,95]

Oropharyngeal candidosis can spread to the larynx and the oesophagus. These manifestations may also occur in the absence of oral disease and are characterised by painful swallowing or stridor.[7,96,97] The diagnosis of oesophageal candidosis is typically suspected in patients with oral infection and difficult swallowing. The diagnosis can be established by culture or histopathology from samples obtained by endoscopy but usually patients are treated when symptoms suggest oesophageal candidosis and typical oral manifestations are seen. Endoscopy with culture and histopathology is needed when patients treated empirically do not respond to antifungal therapy.[2]

The diagnosis of infections of the skin, hair and vulvovaginal candidosis should be confirmed by microscopy and culture. Details on the diagnosis and management of these entities can be found in the clinical guidelines provided by the 'Deutschsprachige Mykologische Gesellschaft' which can be accessed via the AWMF homepage.[90,98,99]

Candidaemia is the most frequent manifestation of deeply invasive candidosis. Pyrexia is typically found. Often the infection is associated with intravenous catheters. The serious prognosis associated with candidaemia is highlighted by a recent survey of 60 cases with candidaemia due to *C. albicans* (n = 38) and non-albicans (n = 22): 8% developed severe sepsis and 27% septic shock. The all cause mortality was 42%.[100]

The term acute disseminated candidosis is not widely used in Europe. This entity is found in patients with malignancy and prolonged granulocytopenia. Patients present with sepsis, persisting candidaemia, haemodynamic instability and disseminated skin or organ involvement. It is associated with a high mortality.[2,7,96,101] Chronic disseminated candidosis (e.g. hepatosplenic candidosis) is also found in patients with malignancy typically after recovery from granulocytopenia. Patients present with persisting fever after bone marrow recovery, a liver that is painful on palpation, elevated alkaline phosphatase (AP) and subsequently focal lesions of the liver, spleen, sometimes the kidneys and lungs as demonstrated by ultrasound, CT or MRI. Blood cultures frequently remain negative in this entity.[2,19,102–105]

Other manifestations of invasive candidosis such as meningoencephalitis, osteomyelitis, endocarditis, end-

ophthalmitis and peritonitis are infrequently found. Clinical symptoms are determined by the affected organs and the extent of organ involvement.[7,96,97,101]

Diagnosis

The diagnosis of systemic candidosis is based on the cultivation of yeast from sterile clinical specimens or the demonstration of yeast by histopathology from infected tissue.[106] Yeast of the genus *Candida* are saprophytes, ubiquitous on the skin and mucous membranes. Yeast cultured from sterile specimens should always be identified to the species level. *In vitro* resistance testing should be performed from all isolates recovered from invasive infections. The distinction between colonisation and infection is not possible when yeast are cultured from non-sterile specimens such as sputum.

Microbiology

Culture

A number of studies in the ICU setting have documented that the colonisation of more than one body site is associated with invasive infection.[107–110] The magnitude of colonisation can be quantified by the Candida-Colonisation-Index (CCI) (see Fig. 1a). A CCI > 0.5 precedes a systemic infection by 6 days; the positive predictive value (PPV) was 66%, the negative predictive value (NPV) 100%.[107] The inclusion of the quantity of colonising yeast (corrected colonisation index, cCCI) (see Fig. 1a) further increased the usefulness of the index with a PPV and NPV of 100%.[107] Cultivation of *Candida* from one or two body sites (urine and stool) only was not a predictor for candidaemia.[21] A prospective French study showed that pre-emptive antifungal therapy based on the cCCI significantly reduced the rate of candidaemia.[111] Based on these data, some experts recommend the routine use of monitoring the colonisation with yeast in intensive care unit patients.[109] By adding of clinical risk factors for invasive *Candida* infections to the CCI, Leon evaluated a '*Candida* score' for the prediction of invasive infections in prospective cohort studies.[112,113] The score includes the colonisation with *Candida*, previous surgery, total parenteral nutrition and the presence of severe sepsis (see Fig 1b). A score ≥3 was highly predictive for invasive candidosis.[114]

Blood cultures are the method of choice for the diagnosis of candidaemia. Two pairs of blood culture bottles (10 ml each) should be obtained for aerobic and anaerobic culture when candidaemia is suspected before the initiation of antifungal therapy.[115] Using this approach, about 90% of candidaemia episodes can be detected. It appears that the detection of *C. glabrata* is enhanced in anaerobic media. To increase the yield of blood cultures above 95%, up to four blood culture pairs have to be obtained in 24 h.[116] However, this approach is not routinely used. Standard blood culture media detect most *Candida* species. The addition of special fungal media may further enhance the speed and recovery of yeast from blood ('Mycosis-IC/F-Medium' or BacT/ALERT 3D).[117–119] However, a separate blood culture bottle has to be used for this procedure.

About 30–40% of all episodes of candidaemia are associated with intravenous catheters.[109,115,120–122] In patients with central venous lines and suspected candidaemia, one pair of blood cultures should be obtained via the central line and from a peripheral site. A distinction between catheter-associated and non-catheter-associated candidaemia might be achieved by comparing the time to positivity [time to positivity (TTP); 17 vs. 38 h] or by comparing the number of CFUs from the blood drawn via the catheter and the peripheral blood.[123,124] In cancer patients, outcome of candidaemia was correlated with time to positivity in blood cultures.[125]

(a)

$$\text{CCI} = \frac{\text{Number of body regions colonised with Candida}}{\text{Number of regions tested per patient}}$$

$$\text{cCCI} = \text{CCI} \times \frac{\text{Number of body regions with high numbers of Candida *}}{\text{Number of body regions per patient colonised with Candida}}$$

(b)

Multifocal *Candida* Colonisation	= 1 point
Parenteral nutrition	= 1 point
Severe sepsis	= 2 points
Major surgery	= 1 point

Figure 1 (a) *Candida* Colonisation Index (CCI/cCCI; according to Pittet *et al.*, [107]). *High numbers $>10^5$ CFU ml^{-1}. (b) *Candida* (Leon) score.[112,114] Points need to be added and a cumulative score of ≥3 is asscociated with invasive candidosis.

In patients with chronic disseminated candidosis, cultures frequently remain sterile. Depending on patient characteristics, the number of blood cultures, the cultured volume and the culture detection system used, the sensitivity ranges between 40% and 68%.[109,115,126]

Growth of *Candida* from urine is typically associated with urinary catheters. A distinction between colonisation and urinary tract infections by *Candida* might be facilitated by the quantification of yeast in the urine. The cultivation of a high number of colony forming units (CFUs), the presence of leucocyturia and symptoms of a urinary tract infection favours the presence of a urinary tract infection vs. a colonisation. The cultivation of more than 100 000 yeast per ml of urine or more than 1000 yeast per ml of urine collected by a sterile disposable catheter is used as a cut off for the diagnosis of infection.[2,127] When yeast are cultivated from respiratory specimens, a distinction between colonisation and infection is not possible. As invasive respiratory infections are only rarely caused by *Candida* spp., the cultivation of *Candida* from respiratory infections alone does not prove an invasive infection.[115,128] However, the cultivation from respiratory sites is important when it is part of a multi-site colonisation as a basis for pre-emptive treatment strategies using the CCI or cCCI.[109]

In vitro susceptibility testing (determination of the minimal inhibitory concentration, MIC) is indicated for all isolates from blood and other sterile specimens. MIC testing can be performed for all antifungals by standardised techniques. The most frequently used techniques are the North American standard (CLSI M27-A3/S3), the European standard (EUCAST) and in Germany the DIN-method.[129–137] Only the US standard (CLSI M27-A3/S3) defines breakpoints for the distinction of susceptible and resistant organisms for the most frequently used antifungals (see Tables 6 and 7). The European standard (EUCAST) and the DIN-standard define breakpoints for fluconazole and voriconazole only. As all these protocols use labour-intensive microdilution methods, alternatives such as the E-test are frequently used in clinical care.

The correlation between the MIC and response to antifungal therapy was established for the treatment of oropharyngeal candidosis with fluconazole. The correlation is less established in the treatment of invasive candidosis with fluconazole or voriconazole.[134,138–140] Newer data suggest a correlation between the MIC, the fluconazole dosage and the area under the curve (AUC) as a marker for drug exposure and the therapeutic efficacy.[141,142] There are currently no data that suggest a predictive value of the MICs for the treatment outcome when amphotericin B and echinocandins are used to treat systemic candidosis. Despite this, the current North American standard (CLSI M27-A3) suggests MIC breakpoints for these antifungals.[135]

Non-culture methods

The identification of cultured yeast to the species level needs 1–3 days depending on the identification method used. A commercial assay based on fluorescence *in situ* hybridisation [peptide nucleic acid fluorescent *in situ* hybridisation (PNA FISH); e.g. Yeast Traffic Light™ (AdvanDx, Inc., Vedbaek, Denmark) PNA FISH™] allows for a rapid presumptive differentiation between *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*, the most commonly cultured agents of candidaemia recovered from blood cultures.[143] Recently, matrix-assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF MS) has been described for rapid routine identification of clinical yeast isolates with high diagnostic accuracy and reliability.[144]

Serological tests may be used as adjunctive diagnostic tests. A commercially available latex agglutination test (e.g. Cand-Tec®-Test; Ramco Laboratories, Houston, TX, USA), detects a *Candida* antigen not thoroughly characterised. Sensitivity (30–77%) and specificity (70–88%) varies widely between different studies. False positive results have been described in the presence of rheumatoid factor and in patients with impaired renal function.[145–150] The monoclonal antibody EB-CA1 binds to mannan-epitopes of different human-pathogenic *Candida* species. It is commercially available as latex-agglutination (Pastorex-*Candida*; BioRad, BioRad Laboratories GmbH, Munich, Germany) or as a Sandwich-ELISA (Platelia-*Candida*; BioRad). Both have comparable specificity (70–80%), but the ELISA shows an improved sensitivity (42–98%).[151,152] Further improvements in the sensitivity (76%) can be achieved by the combination of the sandwich ELISA with the detection of specific antibodies (Platelia-*Candida*).[148,149] The early increase of mannan antigen and anti-mannan antibodies was suggested as helpful for the diagnosis of hepatosplenic candidosis.[153]

The detection of circulating 1,3-beta-D-Glucan (e.g. Fungitell® Assay; Cape Cod, MA, USA) from the cell wall of yeast has been suggested for the diagnosis of invasive candidosis. A correlation between antigenemia and disease outcome was established in animals as well as in patients with invasive candidosis. So far, clinical data are not sufficient to define the clinical usefulness of the test. The test cannot distinguish between infections caused by different fungal agents such as *Candida*, *Aspergillus* and *Pneumocystis jirovecii*.[154–156]

The use of PCR for the diagnosis of invasive candidosis has been evaluated for 20 years but is not yet part of the routine diagnostic. The detection of DNA from *Candida* in body fluids and from blood cultures were the first attempts to use molecular methods for the diagnosis of fungal infections. Buchman *et al.* were the first to describe a method to amplify DNA from *C. albicans* in urine, wound secretions, respiratory tract specimens and blood from surgical patients in 1990.[157] Since then, a number of protocols have been published that improved the specificity of primers and probes and the PCR platform. However, no single assay has been established as a standard assay.[158–169]

Recently, a number of commercial assays have been introduced that allow the molecular detection of *Candida* (and other fungi) in blood (e.g. Lightcycler Septifast-Test, Roche Diagnostics GmbH, Mannheim, Germany). As for the serological methods, the clinical validation of these assays is insufficient to define their role in patient management.[170] However, the speed of molecular methods may provide a prognostic benefit.

Tissue examination

A definite diagnosis of proven systemic candidosis requires histological and/or cultural evidence from tissue samples or resection material.

In rare entities such as hepatosplenic candidosis (HSC), microscopy may detect fungal elements in up to 50% of samples. However, culture is rarely positive in HSC, even in samples positive by microscopy.[20,171] Whether molecular methods improve this yield is not yet clear but they should be used in difficult cases.[172] False negative results have been described in samples obtained by needle aspiration of hepatic lesion in patients with hepatosplenic candidosis and laparoscopic guidance has been suggested to improve the rates of detection.[173] The sensitivity of biopsy might be highest during the first three weeks after bone marrow regeneration.

Diagnostic imaging

Ultrasound-, computed tomography (CT) and magnetic resonance imaging scans (MRI) are important tools for the diagnosis of invasive candidosis (e.g. HSC), the monitoring of treatment response and as a guide for obtaining biopsies. Studies comparing the different methods are difficult to interpret because of differences in technology and experience of investigators. Whereas ultrasound is useful for screening and follow up studies, a negative result does not exclude invasive mycosis. Therefore, an additional MRI scan might be needed to diagnose HSC or other forms of invasive candidosis.[103–105,174,175]

Hepatosplenic candidosis in patients with malignancy after recovery from granulocytopenia is characterised by small abscessed lesions in liver, spleen and sometimes other organs.[174–178] Other disease entities (e.g. CNS abscess) do not show characteristic results in imaging studies and therefore require tissue biopsies to characterise the aetiology of lesions.

Therapy

Currently, antifungal agents from four different groups are licensed for the treatment of invasive fungal infections: polyenes, azoles, echinocandins and nucleoside analogues.

The list of licensed antifungals of the polyene class consists of amphotericin B deoxycholate (D-AMB), the lipid formulations of amphotericin B (liposomal amphotericin B (L-AMB), amphotericin B lipid complex (ABLC) and amphotericin B colloidal dispersion (ABCD). ABCD is licensed in some countries (e.g. Austria) but not in Germany. Mixtures of D-AMB with fat emulsions (e.g. Intralipid®, Fresenius Kabi, Graz, Austria) are not licensed and should therefore not be used.[179,180]

Additional antifungals used for systemic therapy include the triazoles fluconazole, itraconazole, posaconazole and voriconazole, the echinocandins anidulafungin, caspofungin and micafungin and the nucleoside analogue flucytosine. Flucytosine is only used as a part of a combination regimen because of the rapid emergence of resistance.[181,182] Flucytosine is the only systemically used antifungal for which therapeutic drug monitoring is established to avoid toxic effects.[182,183] However, data are emerging that suggest the potential usefulness of therapeutic drug monitoring when itraconazole, posaconazole and voriconazole are used in prophylactic or therapeutic regimens.[184–186]

Detailed descriptions of the pharmacology of systemic antifungals can be found in recent reviews and the prescribing information.[187,188]

Table 3 provides an overview on important pharmacological characteristics of antifungals. Tables 4 and 5 describe dosing in patients with renal- and hepatic insufficiency.

Important considerations when choosing the antifungal agent and the mode of application (i.v. vs. oral) in systemic candidosis include the localisation of the infection, the severity of disease (e.g. sepsis and septic shock), impairment of organ functions (especially liver and kidney), previous exposure to antifungals, the identified fungal strain, local resistance patterns and patient characteristics such as age. In

Table 3 Pharmacokinetics of systemic antifungal agents for the treatment of superficial and systemic *Candida* infections.

Parameter	AMB	5-FC	FCZ	ITZ	PCZ	VCZ	ANID	CAS	MICA
Mode of administration	i.v.	i.v./(p.o.)[1]	p.o./i.v.	p.o./i.v.	p.o.	p.o./i.v.	i.v.	i.v.	i.v.
Dose linearity	[3]	+	+	–	?	–	+	+	+
Oral availability (%)	N/A	>90	>90	>50	>50	>90	N/A	N/A	N/A
Plasma protein binding (%)	[3]	10	12	>99	>95	58	84	97	99
Volume of distribution (l kg^{-1})	[3]	0.7	0.7	>5	>5	2	0.7	N/A	0.25
Elimination half-life (h)	Days	6	30	<40	25	6	24	8–10	15
Substrate/inhibitor of cytochrome-P450-enzymes	–	–	3A4 1A2 2C9,10,19	3A4 1A2 2C9	3A4[2]	3A4 2C9 2C19	–	–	–
Route of elimination	E, U/F	E, U	E, U	M, F > U	E, F > U	M, U > F	D, F	D/M U > F	M F > U

AMB, amphotericin B; 5-FC, flucytosine or 5-flucytosine; FCZ, fluconazole; ITZ, itraconazole; PCZ, posaconazole; VCZ, voriconazole; ANID, anidulafungin; CAS, caspofungin; MICA, micafungin; E, excretion unchanged; M, metabolisation; D, degradation; U, urine; F, faeces; ?, dose linearity is unclear for posaconazole

[1]p.o. available in Germany via import.

[2]Only inhibitor, no substrat.

[3]Depending on the carrier.

Table 4 Dosage recommendations in adult patients with candidaemia and renal insuciency.

		GFR ml min^{-1} (MDRD)				
		>50	10–50	<10		
Amphotericin B deoxycholate (D-AMB)	0.7–1.0 mg kg^{-1} day^{-1}	100%[1]				
Liposomales amphotericin B (L-AMB)	3 mg kg^{-1} day^{-1}	100%				
AMB lipid complex (ABLC)	5 mg kg^{-1} day^{-1}	No data available[1]				
AMB colloidal dispersion[1] (ABCD)	3–4 mg kg^{-1} day^{-1}	100%[1]				
Flucytosine	4 × 25 mg kg^{-1} day^{-1}	Two times 50% per day[2]		Single dose 100%[2]		
Caspofungin	Day 1, 70 mg day^{-1} From day 2, 1 × 50 mg day^{-1}	100%				
Micafungin	1 × 100 mg day^{-1}	100%				
Anidulafungin	Day 1, 200 mg day^{-1} From day 2, 100 mg day^{-1}	100%				
Fluconazole	400–800 mg day^{-1}	100%	50%	50%	50%[3]	50%
Itraconazole	Day 1–2, 2 × 200 mg From day 3, 1 × 200 mg	100%	Not indicated when GFR is below 30 ml min^{-1}			
Voriconazole	Day 1, 2 × 6 mg kg^{-1} day^{-1} From day 2, 2 × 3 mg kg^{-1} day^{-1}	100%[4]				
Posaconazole	4 × 200 mg day^{-1}	100%				

GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease (formula).

[1]Should not be used in renal insufficiency.

[2]Therapeutic drug monitorring needed when GFR <20 ml min^{-1}, therapeutic range: 25–50 mg l^{-1}. bone marrow suppression more frequent in renal insufficiency.

[3]Administration after haemodialysis (HD).

[4]Due to acumulation of the carrier when GFR <55 ml min^{-1} i.v. for 14 Tage only recommended, no limitation for oral administration.

addition, contraindications and warnings summarised in the respective prescribing information need to be considered.

All antifungals have good activity against a broad range of *Candida* spp, especially *C. albicans*. Some non-*Candida albicans* spp are characterised by special susceptibility patterns to antifungals, e.g. *C. krusei* is resistant against fluconazole but susceptible for voriconazole. About 30% of *C. glabrata* isolates show a reduced susceptibility for fluconazole and other azoles, another 30% are *in vitro* resistant to fluconazole with variable cross resistance for other triazoles.

Table 5 Dosage recommendations for adult patients with candidaemia and hepatic insuciency.

		Child Pugh Score		
		A	B	C
Amphotericin B deoxycholate (D-AMB)	0.7–1.0 mg kg^{-1} day^{-1}	[1]	[1]	[1]
Liposomales amphotericin B (L-AMB)	3 mg kg^{-1} day^{-1}	[1]	[1]	[1]
Amphotericin B lipid complex (ABLC)	5 mg kg^{-1} day^{-1}	[1]	[1]	[1]
Amphotericin B colloidal dispersion (ABCD)	3–4 mg kg^{-1} day^{-1}	[1]	[1]	[1]
Flucytosine	4 × 25 mg kg^{-1} day^{-1}	No clinical data		
Caspofungin	Day 1, 70 mg day^{-1} loading From day 2, 1 × 50 mg day^{-1}	No dose adjustment	Dose reduction to 35 mg day^{-1} ab CHILD 7–9 (according to prescribing information)	
Micafungin	1 × 100 mg day^{-1}	No dose adjustment		Not recommended (according to prescribing information)
Anidulafungin	Day 1, 200 mg day^{-1} loading From day 2, 100 mg day^{-1} Erhaltung	No dosage adjustment		
Fluconazole	400–800 mg day^{-1}	Loading dose unchanged, maintenance dose 50% reduced		No clinical data
Itraconazole	Day 1–2, 2 × 200 mg i.v. loading From day 3, 1 × 200 mg	No clinical data		
Voriconazole	Day 1, 2 × 6 mg kg^{-1} day^{-1} loading From day 2, 2 × 3 mg kg^{-1} day^{-1} Erhaltung	Loading dose unchanged, maintenance dose 50% reduced		No clinical data
Posaconazole	4 × 200 mg day^{-1}	No clinical data		

[1]No recommendations due to insufficient data.

Table 6 Breakpoints for *in vitro* resistance testing of *Candida* spp. against systemic antifungals according to 'Reference Method for Broth Dilution Antifungal Susceptibility testing of Yeasts. Approved Standard M27-A3/S3' of Clinical Laboratory Standards Institutes (CLSI).[135,376]

Drug	Susceptible (S)	Susceptible, dose dependend (S-DD)	Intermediate (I)	Resistant (R)	Not susceptible (NS)
Anidulafungin	≤2	–	–	–	>2
Caspofungin	≤2	–	–	–	>2
Fluconazole	≤8	16–32	–	≥64	–
Flucytosine	≤4	–	8–16	≥32	–
Itraconazole	≤0.125	0.25–0.5	–	≥1	–
Micafungin	≤2	–	–	–	>2
Voriconazole	≤1	2	–	≥4	–

No breakpoints have been determined for amphotericin B and posaconazole. For echinocandins the category 'not susceptible' has been introduced.

Candida lusitaniae has a variable *in vitro* susceptibility for D-AMB and the MICs for the echinocandins of *C. parapsilosis* and *C. guilliermondi* are higher than for other *Candida* species[189,190] (see Tables 6 and 7).

Candidaemia

The preferred antifungal therapy for candidaemia and other systemic *Candida* infections is either fluconazole (400–800 mg day^{-1} i.v.; double dose as 'loading

Table 7 *In vitro* susceptibility of *Candida* spp. isolates from blood cultures (modified from Ostrosky-Zeichner *et al.*, [189]).

	AMB[1]	5-FC	FCZ	ITZ	VCZ	PCZ[1]	AFG	CFG	MFG
Candida albicans	S	S	S	S	S	S	S	S	S
Candida glabrata	S	S	I-R	S-I-R	S-I-R	S-I-R	S	S	S
Candida tropicalis	S	S	S-I	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	I	I	I
Candida krusei	S	R	R	I-R	S-I-R	S-I-R	S	S	S
Candida guilliermondii	S	S	S	S	S	S	R	R	R
Candida lusitaniae	S-I-R	S	S	S	S	S	S	S	S

Based on resistance testing using the CLSI-M27-A3 method.

AMB, amphotericin B – formulations; 5-FC, flucytosine; FCZ, fluconazole; ITZ, itraconazole; VCZ, voriconazole; PCZ, posaconazole; AFG, anidulafungin; CFG, caspofungin; MFG, micafungin; S, susceptible; I, intermediate; R, resistant.

[1]No breakpoints have been determined for amphotericin B and posaconazole.

Table 8 Dosage recommendations for adults with candidaemia.

Antifungal drug	Dosage	Evidence	Comment
Monotherapy			
Polyenes			
Amphotericin B deoxycholate (D-AMB)	0.7–1.0 mg kg^{-1} day^{-1}	C-I	[191,200]
Liposomal amphotericin B (L-AMB)	3 mg kg^{-1} day^{-1}	A-I	[195]
Amphotericin B lipid complex (ABLC)	5 mg kg^{-1} day^{-1}	C-II	[220]
Amphotericin B colloidal dispersion (ABCD)[4]	3–4 mg kg^{-1} day^{-1}	C-III	[377,378]
Echinocandins			
Anidulafungin	Day 1, 200 mg day^{-1} loading From day 2, 100 mg day^{-1}	A-I	[194]
Caspofungin[2]	Day 1, 70 mg day^{-1} loading From day 2, 1 × 50 mg day^{-1}	A-I	[193]
Micafungin	1 × 100 mg day^{-1}	A-I	[195]
Azoles			
Fluconazole	400–800 mg day^{-1}	A-I	[191,192]
Itraconazole	Day 1–2, 2 × 200 mg i.v. loading From day 3, 1 × 200 mg	C-III[1]	[379]
Posaconazole	4 × 200 mg day^{-1}	C-III	No data
Voriconazole	Day 1, 2 × 6 mg kg^{-1} day^{-1} loading From day 2, 2 × 3 mg kg^{-1} day^{-1}	A-I	[200]
Others			
Flucytosine	4 × 25 mg kg^{-1} day^{-1}	In combination with polyenes only. Therapeutic drug monitoring	[182]
Combination therapy			
Amphotericin B deoxycholate and fluconazole	0.7 mg kg^{-1} day^{-1} 800 mg day^{-1}	B-I	[192]
Amphotericin B lipid complex or liposomal amphotericin B (with Efungumab[3])	1 × 5 mg kg^{-1} day^{-1} (or) 1 × 3 mg kg^{-1} day^{-1} (1 mg kg^{-1} day^{-1} dose 1–5)	C-III	[214,380]
Amphotericin B deoxycholate and flucytosine	0.7–1.0 mg kg^{-1} day^{-1} and 4 × 25 mg kg^{-1} day^{-1}	C-III	[212]

[1]Data not available in peer reviewed format; no licensed indication.

[2]In patients with more than 80 kg, maintenance is 70 mg day^{-1}.

[3]Efungumab is not yet licensed by the EMEA/FDA and not available.

[4]ABCD is not licensed in Germany.

dose' on day 1) or an echinocandin, such as anidulafungin (200 mg 'loading dose', then 100 mg day^{-1} i.v.), caspofungin (70 mg 'loading dose', then 50 mg day^{-1} i.v.) or micafungin (100 mg day^{-1} i.v. without 'loading dose')[191–195] (AI) (see Table 8).

Fluconazole has been evaluated in two randomised clinical trials using dosages of 400 mg day^{-1} or 800 mg day^{-1} (+/− AmB-D). Whether the higher dosage leads to increased clinical efficacy is unknown.[191,192] Fluconazole should not be used in breakthrough infections in patients receiving prophylactic azoles or in infections due to *C. glabrata* and *C. krusei* because the *in vitro* susceptibility might be reduced (*C. glabrata*) or because of resistance (*C. krusei*).[189] A direct comparison between fluconazole and anidulafungin showed a similar safety profile, a better treatment response and a trend towards better survival in patients treated with anidulafungin.[194] Empiric therapy with fluconazole should not be used in critically ill, septic patients. Instead, an echinocandin or liposomal amphotericin B should be used in these patients.

A direct comparison of caspofungin and micafungin showed similar efficacy and safety. In addition, no difference in safety or efficacy was seen in patients treated with two different dosages of micafungin (100 mg day^{-1} or 150 mg day^{-1}).[196] Further studies comparing different echinocandins are lacking. Higher dosages of caspofungin (150 mg day^{-1} vs. 70/50 mg day^{-1}) and micafungin (150 mg day^{-1} vs. 100 mg day^{-1}) showed a trend towards improved efficacy in subgroups of patients (APACHE-II score >20, granulocytopenia) and might be used in selected patients[196,197] (BIII). As a result of increased MICs and a higher rate of persistent fungaemia, the use of echinocandins in candidaemia due to *C. parapsilosis* may not be regarded as therapy of first choice.[189,190,193,194,198,199] As a result of alterations of hepatocytes [foci of altered hepatocytes (FAH)] and hepatic tumours observed in rats exposed to micafungin for extended periods of time, micafungin should only be used after careful consideration of benefits and risks. The clinical relevance of these findings is unknown. Comparable long-term safety data have not been obtained for the other echinocandins.

As an alternative to fluconazole or the echinocandins, liposomal amphotericin B (L-AMB, 3 mg kg^{-1} day^{-1} without 'loading-dose') or voriconazole (2 × 6 mg kg^{-1} day^{-1} i.v. 'loading dose', then 2 × 4 mg day^{-1})[195,200] may be used as antifungal therapy for invasive candidosis. L-AMB has a higher rate of nephrotoxicity compared with the triazoles and the echinocandins. Voriconazole (and itraconazole) has a higher potential for drug–drug interactions via cytochrome p450-dependent enzymes than fluconazole, the echinocandins or liposomal amphotericin B.[201,202]

Itraconazole and posaconazole have not been studied in candidaemia to justify their use in this indication. The use of D-AMB is associated with significant toxicity (infusion-related electrolyte imbalances and nephrotoxicity) and its use is therefore discouraged outside resource poor settings as a first line agent for the treatment of invasive candidosis.[31,32,106,203–209] Continuous infusion (24 h) of amphotericin B deoxycholate is better tolerated, but the efficacy has not been documented in randomised trials and therefore, it should not be used.[210]

As a result of the lack of data from randomised clinical trials, the combination of D-AMB (0.7–1.0 mg kg^{-1} day^{-1}) with flucytosine (100 mg kg^{-1} day^{-1}, divided in 3–4 doses) is only recommended for certain disease entities (endocarditis, meningitis, peritonitis and arthritis)[2,211–213] (B-III). The combination of D-AMB (0.7 mg kg^{-1} Tag^{-1}) with fluconazole (800 mg Tag^{-1} i.v.) was compared with monotherapy with fluconazole (800 mg Tag^{-1} i.v.) in a randomised clinical trial. The combination treatment showed a significantly improved microbiological response (69% vs. 56% $P = 0.043$), but a significant higher rate of nephrotoxicity (23% vs. 3%) as well.[192] A randomised clinical trial comparing lipid-associated amphotericin B (L-AMB or ABLC) monotherapy and a combination of either lipid-associated amphotericin B with a heat shock protein (HSP-) 90-antibody inhibitor (Mycograb) showed a favourable response of the combination therapy.[214] However, this monoclonal antibody is not currently available for clinical use. Other combinations of currently licensed antifungals have not been studied.

Every blood culture that reveals growth of yeast together with clinical signs of infections represents an infection that needs prompt management including the initiation of antifungal therapy (A-I) and the removal of central venous lines (A-II). When cultures of only a catheter tip grow yeast, while blood cultures remain sterile, systemic antifungals are not indicated in every case, depending on the clinical condition of the patient.[215] Rapid initiation of correctly dosed antifungals is critical for patient prognosis[41,42,216] (A-II). Whether pre-emptive treatment strategies in febrile non-granulocytopenic ICU patients improve the outcome is not proven.[109,217] The prophylactic use of antifungals is beyond the scope of this manuscript. However, a meta-analysis of studies in non-granulocytopenic ICU patients documented a reduction in mortality of 24% and a reduction in the incidence of invasive fungal infections of 50% in patients treated with prophylactic fluconazole or ketoconazole.[218] Ketoconazole is not used for this indication, but fluconazole may be an option for selected high-risk patients.[219] Beside the importance of early antifungal

therapy, other prognostic factors have been determined, such as the underlying disease, the severity of the illness (APACHE-II-Score), the amount of immunosuppression, advanced age and impairment of the renal function.[192,216] By contrast, the prognosis appears not to be affected, whether a polymicrobial (e.g., isolation of more than one *Candida* spp) or monomicrobial aetiology is determined. Therefore therapy is not different, especially when an echinocandin is used.[85]

In accordance with other guidelines, antifungal treatment for uncomplicated candidaemia is recommended for 14 days after the first negative blood culture and resolution of all clinical signs of infection.[2] This recommendation is derived from the duration used in clinical registration trials. Therefore, drawing of blood cultures is recommended after initiation of antifungal therapy. In clinical trials, the mean duration of antifungal therapy is 12–16 days (up to 66 days in selected cases). Therefore, if follow up cultures are not available, antifungal treatment should be continued at least for 14 days after the last positive blood culture and all clinical signs of infection have resolved.[193–196,200] In most clinical trials, the median time to the first negative blood culture was 2–3 days. Persistent positive blood cultures in clinically stable patients with susceptible organisms (MIC testing) until day 3 after the start of antifungal therapy and removal of central venous lines may not reflect treatment failure, as 20% of successfully treated patients still have positive blood cultures at day 3.[193,200] However, in clinically unstable patients, antifungal treatment should be changed in the absence of clinical improvement after day 3–4 (C-III). In patients failing antifungal therapy, deep tissue involvement should be excluded, the class of antifungals should be switched or a combination therapy with two *in vitro* active drugs be started (CIII). Treatment failure can be defined as persisting positive blood cultures for more than 3 days in the absence of clinical improvement or a worsening of clinical signs (B-II). Potential invasive (tissue) infection causing treatment failure with persisting or relapsing candidaemia include catheter or implant associated infections, endocarditis, peritonitis, bone infections or abscesses which must be excluded in these cases.

If clinically feasible, immunosuppressive therapy should be reduced or stopped (B-III).[216] Fundoscopy should be performed in all patients with invasive candidosis before antifungal therapy is discontinued to exclude chorioretinitis[2] (B-III). Further tests, such as ultrasound or echocardiography are not routinely indicated in uncomplicated candidaemia.

After improvement of clinical signs, sterilisation of blood cultures and documented *in vitro* susceptibility of the causative yeast, step down therapy after initial treatment with an echinocandin (anidulafungin, caspofungin and micafungin) was shown to be effective with oral fluconazole starting on day 10 or in another study with D-AMB compared with voriconazole on day 4 of antifungal therapy, and may be recommended if oral drug intake and gastrointestinal absorption is possible[193,194,196,200] (B-III).

Candidaemia in granulocytopenic patients

Although data are limited, the response to antifungal therapy is reduced by 15–20% in the granulocytopenic host.[193,195,196] The clinical response to amphotericin B lipid complex was reduced by 20–30% in patients who where granulocytopenic at diagnosis or became granulocytopenic after diagnosis when compared with the whole cohort consisting of granulocytopenic and non-granulocytopenic patients included in a large cohort study [Collaborative Exchange of Antifungal Research (CLEAR) database].[220] To reduce the duration of granulocytopenia, G-CSF or GM-CSF may be used in granulocytopenic patients (C-III).[221] In animal models of systemic fungal infections, the use of G-CSF in addition to antifungals showed a positive effect, presumably by improving the function of neutrophils.[222] Selected granulocytopenic patients may benefit from the infusion of granulocytes.[223] However, the routine use of G-CSF/GM-CSF or the infusion of granulocytes is not recommended as standard therapy (C-III).

A randomised clinical trial[32] and a cohort study[31] did not show a significant difference in antifungal efficacy between fluconazole and amphotericin B deoxycholate in granulocytopenic patients with systemic candidosis. However, the number of patients was small and there was a trend to a lower response to antifungal treatment in patients with neutrophil counts below 1000 μl^{-1} treated with fluconazole when compared with amphotericin B. Therefore, fluconazole is not recommended as first line therapy in granulocytopenic patients. Although D-AMB, anidulafungin, caspofungin or micafungin have been tested in controlled clinical trials,[193–195] the number of granulocytopenic patients in these trials was limited. For voriconazole, only data from salvage therapy studies are available.[224] Given the high rate of infections due to non-*Candida albicans* yeast in granulocytopenic patients and the importance of a fungicidal mode of action, echinocandins or liposomal amphotericin B are preferred as the first line therapy for systemic candidosis in granulocytopenic patients (B-III).

In addition to fundoscopy, an abdominal ultrasound (liver, spleen and kidneys) should be performed in

granulocytopenic patients with candidaemia after bone marrow recovery to exclude chronic disseminated infection/hepato-splenic candidosis that may not be associated with clinical symptoms other than fever (B-III).

Acute disseminated candidosis

Acute disseminated candidosis is the most severe form of systemic candidosis in granulocytopenic patients. It is characterised by haemodynamic instability, persistent positive blood cultures and deep organ and/or skin involvement. In i.v. drug users, a comparable disease entity may become symptomatic only hours after i.v. drug use. Patients present with sepsis, spiking fever, shaking chills and disseminated lesion of the skin and sometimes other organ infections such as endophthalmitis or osteomyelitis.[225,226] Contamination of the drugs or solvents used is being discussed as potential sources of yeast.[227] Echinocandins or liposomal amphotericin B is recommended as initial antifungal treatment (B-III). In this condition, fluconazole is not recommended (C-III). The duration of treatment depends on the clinical response to treatment and the time to elimination of *Candida* from bloodstream. No definite duration of antifungal therapy has been established.

Management of intravenous lines

Central venous lines should be regarded as an infectious focus and should be removed whenever possible, regardless if they are the primary portal of entry or if they are secondarily colonised[2,228] (A-II). A rapid sterilisation of the bloodstream is only achieved by the removal of infected central venous lines including implanted catheters (Port-/Hickman/Broviac-Systems). Removal should be performed with the initiation of antifungal therapy. If the central venous lines are retained, the duration of candidaemia increases (from 3 to 6 days) as does the mortality of patients.[21,216,228,229] This is particularly supported by data for infections due to *C. albicans* and *C. parapsilosis*, but less for other *Candida* species. The best time for removal is controversial but should generally be performed as early as possible.[230] The role of catheter removal in granulocytopenic patients is particularly controversial as the gastrointestinal mucosa, damaged by cytotoxic chemotherapy, is thought to be the main port of entry for yeast to the bloodstream.[208,231,232] However, as the central venous line might be colonised, it is recommended to remove them in these patients (B-III).

Whether the superior activity of echinocandins and liposomal amphotericin B against biofilms on catheters, as shown in *in vitro* models compared with fluconazole, is clinically relevant is not proven.[233–235] Data from clinical trials do not answer this question and as long as no new data emerge from clinical trials, removal of catheters is recommended[193–196] (B-II).

Paediatric patients

Concerning the choice of the antifungal agent and the disease management, the same rules as for adults apply for paediatric patients. The reduced or missing activity of fluconazole to *C. glabrata* and *C. krusei*, previous exposure to antifungals, potential side effects, interactions of antifungals with other drugs and other information as documented in the prescribing information have to be considered.

As for adult patients, for which most of the clinical data have been collected, central venous lines should be viewed as a potential focus of infection and should therefore be removed. The duration of antifungal therapy in uncomplicated candidaemia is 14 days starting with the last negative blood culture and the resolution of all clinical signs of infection. The duration of antifungal therapy in other systemic *Candida* infections depends on the treatment response. After clinical improvement and the demonstration of *in vitro* susceptibility of the organism, therapy can be switched to oral fluconazole as step down therapy. Fundoscopy should be performed before the end of antifungal therapy in all invasive infections to exclude chorioretinitis.[236]

Paediatric patients beyond the neonatal period

Based on data from paediatric dose finding studies and a randomised clinical trial in systemic *Candida* infections in paediatric patients beyond the newborn period, liposomal amphotericin B or micafungin may be recommended as first line therapy (AI). Other well evaluated therapeutic options include caspofungin (AII) and fluconazole (AII).[237–246] Voriconazole and amphotericin B lipid complex[247,248] are options for second line therapy (AII). As for adults, D-AMB is not considered as a first line therapy of *Candida* infections (CIII). The indications of the combination of D-AMB and flucytosine[182] has not been clearly defined because of a lack of clinical trial data and should therefore not be considered as a standard regimen (CIII) (Dosage recommendations see Table 9).

Newborns and premature neonates

Therapeutic recommendations are based on dose finding studies and small phase II clinical trials and include

Table 9 Dosage of systemic antifungals in paediatric patients beyond the newborn period.[236*]

Indication	Drug/dosage
Superficial infection[1]	Fluconazole (6 mg kg^{-1} day^{-1} q.i.d. p.o./i.v.)
	Itraconazole (2.5 mg kg^{-1} day^{-1} b.i.d. p.o.)[2]
Systemic infection	Caspofungin (50 mg m^{-2} q.i.d. i.v.; day 1: 'loading' 70 mg m^{-2}; max. 70 mg)
	Fluconazole (12 mg kg^{-1} day^{-1} q.i.d. i.v.; max. 800 mg)
	Liposomal Amphotericin B (3 mg kg^{-1} day^{-1} q.i.d. i.v.)
	Micafungin (<40 kg: 2–4 mg kg^{-1} day^{-1} q.i.d. i.v.; ≥40 kg: 100–200 mg day^{-1})
	Second line[3]:
	Amphotericin B deoxycholate (0.7–1.0 mg kg^{-1} q.i.d. i.v.) +/− Flucytosine (100 mg kg^{-1} day^{-1} in 3–4 doses i.v.; TDM needed)[4]
	Amphotericin B lipid complex (5 mg kg^{-1} day^{-1} q.i.d. i.v.)[5]
	Voriconazole (≥12 years: 8 mg kg^{-1} b.i.d. i.v.; day 1: 'loading' 12 mg kg^{-1} b.i.d.; <12 years: 14 mg kg^{-1} day^{-1} b.i.d. i.v.)[5,6]

TDM, therapeutic drug monitoring.

*Alphabetic order, not in order of activity.

[1]Oropharyngeal and vulvovaginal candidosis, *Candida*-Infections of the skin, hair, nails and chronic mucocutaneous candidosis. In refactory cases drugs as for systemic infections.

[2]Not licensed for paediatric patients, Dosage validated in clinical trials.

[3]Due to toxicity/drug--drug interactions/status of licensing.

[4]Status of licensing.

[5]Not sufficiently validated in children below 13 years.

[6]Potential for interactions, benefits compared with fluconazole undefined.

liposomal amphotericin B, amphotericin B lipid complex, caspofungin, micafungin and fluconazole[237,244,249–253] (AII). Amphotericin B deoxycholate is considered as a second line therapy in this patient population (CIII). The role of combination therapy with D-AMB and flucytosine is undefined (CIII) (Dosage recommendations are summarised in Table 10).

Organ infections

The therapeutic approach to invasive organ infections is similar to that of candidaemia combined with surgical resection or debridement of infected tissue. In selected cases, a higher dosage of the antifungal may be indicated (e.g. caspofungin maintenance dose of 100–150 mg instead of 50 mg), but supporting data are limited[197,254] (Recommendations are summarised in Table 11).

Table 10 Dosage recommendations for newborn and preterm newborns.[236*]

Drug	Dosage
Superficial infection[1]	Fluconazole (6 mg kg^{-1} day^{-1} q.i.d. p.o./i.v.)
Systemic infection	Amphotericin B deoxycholate (0.7–1.0 mg kg^{-1} day^{-1} q.i.d. i.v.) +/−
	Flucytosine (100 mg kg^{-1} Tag^{-1} in 3–4 doses i.v.; TDM needed)
	Amphotericin B lipid complex (5 mg kg^{-1} day^{-1} q.i.d. i.v.)
	Caspofungin (25 mg m^{-2} q.i.d. i.v.)
	Fluconazole (12 $mg^{-1}kg$ day^{-1} q.i.d. i.v.)
	Liposomal Amphotericin B (3 mg kg^{-1} day^{-1} q.i.d. i.v.)
	Micafungin (2 mg kg^{-1} day^{-1} q.i.d. i.v.)

TDM, therapeutic drug monitoring.

*Alphabetic order, not in order of activity.

[1]Oropharyngeal and diaper rash.

Central nervous system candidosis

Candida infections of the central nervous system (CNS) may present as meningoencephalitis or as ventriculitis associated with foreign bodies such as shunts or, rarely, brain abscess. As a result of the fungicidal activity of amphotericin, the excellent CSF penetration of flucytosine,[187] documented synergism *in vitro* and *in vivo*,[255] and documented clinical activity in infections due to *Candida*[211] and in cryptococcal meningoencephalitis,[256] many experts prefer the use of D-AMB (0.7–1.0 mg kg^{-1} day^{-1}) with flucytosine (100 mg kg^{-1} day^{-1} in 3–4 doses) as initial therapy (BIII). Data on newer antifungal from clinical trials are not available.[2,257]

Alternative options include liposomal amphotericin B or fluconazole (BIII). The rationale for the use of liposomal amphotericin B (≥5 mg kg^{-1} day^{-1}) is found in studies in experimental *Candida* meningoencephalitis[258] and clinical data from preterm newborns.[250] The efficacy of fluconazole alone or in combination with flucytosine is supported by case reports only.[259] However, the efficacy of fluconazole alone or in combination with flucytosine or D-AMB for cerebral *Candida* infections (e.g. meningitis) is suggested by its proven efficacy in other yeast-associated diseases such as cryptococcal meningitis.[2] Fluconazole, alone or in combination with flucytosine, may be used as an oral consolidation therapy (BIII).

Among the newer antifungals, voriconazole is a reasonable, although unstudied, therapeutic option for *Candida* meningoencephalitis due to good CNS levels[260] and promising data in patients with CNS aspergillo-

Table 11 Treatment of organ infections in adults.

Organ infection	Drug	Dosage	Evidence	Comment
Meningitis/CNS	D-AMB i.v.	0.7–1.0 mg day^{-1}	BIII	[381]
	+ flucytosine	25 mg kg^{-1} q.i.d.	BIII[1]	Tissue penetration of Echinocandins undefined
	L-AMB	3 mg kg^{-1} day^{-1}	BIII[1]	
	Fluconazole[2]	800/400 mg day^{-1}	BIII[1]	
	Voriconazole[2]	8/4 mg kg^{-1} b.i.d.	[1]	
Endophthalmitis/ chorioretinitis	Fluconazole	800/400 mg day^{-1}	BIII	[382] [275]
	Voriconazole	8/4 mg kg^{-1} b.i.d.	BIII	Tissue penetration of Echinocandins undefined
Endocarditis	D-AMB i.v.	0.7–1.0 mg day^{-1}	BII	[284] [282] [287] [288] [254]
	+ flucytosine	25 mg kg^{-1} q.i.d.	BIII	
	Caspofungin	70/50 mg day^{-1}	[1]	
Pneumonia	Anidulafungin	200/100 mg day^{-1}	[1]	Diagnostic confirmation needs histological proof
	Caspofungin	70/50 mg day^{-1}	[1]	
	Fluconazole	800/400 mg day^{-1}	[1]	
	Voriconazole	8/4 mg kg^{-1} q.i.d.	[1]	
Peritonitis	Anidulafungin	200/100 mg day^{-1}	[1]	
	Caspofungin	70/50 mg day^{-1}	[1]	[212]
	Fluconazole	800/400 mg day^{-1}	BII	[213]
	Voriconazole	8/4 mg kg^{-1} b.i.d.	[1]	
	D-AMB i.v.	0.7–1.0 mg day^{-1}	BI	
	+ flucytosine	25 mg kg^{-1} q.i.d.		
Osteomyelitis/ arthritis	Fluconazole	800/400 mg day^{-1}	BII	[383] [325]
	Voriconazole	8/4 mg kg^{-1} b.i.d.	BII	
Candiduria, cystitis, nephritis	Fluconazole	400/200 mg day^{-1}	BI	[384]
Chronic disseminated Candidosis	Fluconazole	800/400 mg day^{-1}	BIII	Step down therapy after 2 weeks of caspofungin/L-AMB with oral fluconazole/ voriconazole/posaconazole
	(if isolate susceptible)	6–12 mg kg^{-1} day^{-1}	BIII	
	Voriconazol	8/4 mg kg^{-1} b.i.d.	BIII	
	Caspofungin	70/50 mg day^{-1}	BIII	
	L-AMB	3 mg kg^{-1} day^{-1}	[1]	

[1]Data difficult to evaluate.

[2]Good CSF penetration of azoles documented but place in primary therapy not well documented, therefore preferred for Step down therapy.

sis.[261,262] Animal models suggest the potential usefulness of the echinocandins in *Candida* meningoencephalitis,[263,264] although higher doses might be required (as studied for micafungin).[265] Clinical data are limited to case reports[240,266] (CIII).

Antifungal therapy for cerebral *Candida* infections is recommended for at least 4 weeks after the resolution of all signs and symptoms of the infection (BIII). In foreign body associated infections of the central nervous system, removal of the foreign bodies is indicated. Brain abscesses usually require neurosurgical intervention.[2]

Candida endophthalmitis and chorioretinitis

Candida infections of the eye include endophthalmitis, chorioretinitis and keratitis. *Candida* endophthalmitis is a rarely diagnosed complication of disseminated *Candida* infection.[267] Older studies have described endophthalmitis (e.g. 'cotton wool spots') in up to 78% of patients with candidaemia, but recent reports found a much lower incidence.[268–270] In patients treated in a randomised clinical trial (voriconazole vs. amphotericin B), *Candida* chorioretinitis was diagnosed in 9.5%, while endophthalmitis was diagnosed in 1.6%.[200] Of note is the association of i.v. drug abuse, disseminated candidosis and *Candida* chorioretinitis. However, the pathogenesis is not clear.[271,272]

The antifungal therapy of *Candida* chorioretinitis is similar to candidaemia but the treatment is continued until the resolution of all symptoms and signs. Therapeutic options of *Candida* endophthalmitis include D-AMB, alone or in combination with flucytosine (B-III), or as step-down therapy, fluconazole (B-III). Alternative agents include voriconazole or caspofungin but failure of echinocandin therapy have been reported and may occur because of low tissue penetration.[273–275] Case reports also suggest that patients with relevant alterations in visual acuity may benefit from early vitrectomy (e.g. 'pars plana'- vitrectomy), combined with intravitreal application of amphotericin B.[267,276,277]

In animal models of *Candida* keratitis, topical treatment (s.a. fluconazole, micafungin) was successful and this has been confirmed in case reports.[278–280] Systemic therapy of fungal endophthalmitis should be performed using high dosages to maximise antifungal exposure of the infected structures. Treatment should be continued for at least 4–6 weeks until resolution of all signs and symptoms.[2]

Candida endocarditis

The exclusion of *Candida* endocarditis needs repeatedly negative blood cultures and a transesophageal echocardiogramm. This procedure should be performed promptly whenever endocarditis is suspected.[281–283]

The therapy of *Candida* endocarditis includes the surgical removal of affected tissue in combination with antifungal therapy.[284–286] Most published reports on antifungal therapy used D-AMB in combination with flucytosine[282,287,288] for at least 6 weeks after valve surgery (B-III), with an optional consolidation therapy with fluconazole (B-III).

Individual patients with native valve endocarditis, especially due to *C. parapsilosis*, have been successfully treated with fluconazole alone,[259,289] or in combination with liposomal amphotericin B,[290,291] with caspofungin alone or in combination with fluconazole or voriconazole or with continuous infusions of D-AMB.[286,292–296] Among three patients with *Candida* endocarditis treated with higher doses of caspofungin (100 mg day^{-1}), treatment was successful in one case.[254]

Adequate management should include MIC testing of the isolates to exclude *in vitro* resistance, especially in patients with persistently positive blood cultures.[297] This is particularly important in relapsed disease as combined resistance against echinocandins and azoles has been documented during treatment.[297]

Candida endocarditis is a rare disease.[286] Intravenous drug users and immunocompromised patients are susceptible to this infection. Management is particularly difficult when the infectious process is not restricted to the valves, but includes the endocard. It may not be possible to repair the resulting tissue damage. Therefore, management should include antifungal therapy and surgery preferentially during the first 3 weeks after the diagnosis.[284] Surgery is definitely needed in patients experiencing congestive heart failure or thromboembolic events[282] (BIII). As surgery may not be possible in all patients, combination therapy is frequently applied but evidence for its usefulness is restricted to case reports. One case report described the successful treatment of *Candida* endocarditis due to *C. parapsilosis* without cardiac surgery with a combination of caspofungin and voriconazole.[296] (see Tables 6 and 7).

Candida pneumonia and laryngeal candidosis

Candida pneumonia is a rare condition. As yeast are frequently cultivated from respiratory secretions, biopsy of lung tissue is the only reliable means of establishing the diagnosis in patients with pulmonary candidosis.[298,299] However, postmortem studies document pulmonary involvement in up to 50% of patients with disseminated candidosis.[61,300,301] Cultivation of *Candida* spp. from BAL *per se* is no indication for systemic treatment with antifungals or their inhalation. Newer data suggest that even when a colonisation of the respiratory tract with *Candida* spp. is documented by BAL, pneumonia is still rarely present.[128]

Candida pneumonia has mostly been reported in patients with neoplastic diseases.[302–305] The infection is acquired after aspiration of oropharyngeal secretions containing *Candida* spp, or more often after haematogenous dissemination. As a result of a lack of specific treatment trials, therapeutic options are in accordance with candidaemia and acute disseminated candidosis. *Candida* infections of the larynx or epiglottis[306,307] are treated in accordance with the recommendation given above (see Tables 6 and 7).

Candida peritonitis

Candida peritonitis is typically seen in patients undergoing peritoneal dialysis[308,309] or after gut perforation with subsequent secondary or tertiary peritonitis, typically in surgical patients.[310–314] Cultivation of *Candida* from peritoneal swabs or biopsies in patients with secondary peritonitis should be interpreted as evidence for a peritoneal infection with *Candida* spp and should be treated with systemic antifungals.[315]

Recommendations consisted of D-AMB with or without flucytosine or fluconazole, for >2 weeks (B-III). In addition, catheters for peritoneal dialysis should be removed if present,[308,309,314] and adequate surgical interventions are necessary when perforations are suspected (B-III). Concomitant treatment with flucytosine at the start of antifungal treatment is useful because of its favourable pharmacological properties and good antifungal activity (B-III). Newer therapeutic options include caspofungin, anidulafungin, micafungin or liposomal amphotericin B (B-III),[193–195,254] although data on these newer antifungals are restricted to case reports.[316,317]

Optimal duration of peritonitis has not been established but depending on the response to therapy, 2–4 weeks of systemic therapy may be required[2] (B-III) (see Tables 6 and 7).

Candida osteomyelitis and *Candida* arthritis

Debridement, removal of foreign materials in addition to systemic antifungal treatment for 6–12 months is recommended on the basis of the existing literature for the treatment of *Candida* osteomyelitis and *Candida* arthritis caused by fluconazole susceptible yeast[2,318] (BIII). Concomitant therapy with flucytosine at the beginning of systemic antifungal therapy is suggested because of its favourable pharmacological properties and good antifungal activity (*in vitro* synergy and high tissue levels) but clinical data are lacking.[319]

Whether treatment with conventional amphotericin B, lipid-formulations of amphotericin B, voriconazole or one of the echinocandins is associated with therapeutic benefits is unknown. Published data of the use of echinocandins are limited to case reports.[254,320–323] In a case series including patients with systemic candidosis in the absence of candidaemia, treatment with 100–150 mg of caspofungin was successful in four of four patients with osteomyelitis and arthritis.[254] Besides case reports on voriconazole in the treatment of *Candida* bone infections,[324] data on 20 immunocompromised patients with *Aspergillus* osteomyelitis or spondylodiscitis have been published. Most patients received voriconazole as salvage therapy for a median treatment duration of 83 days (range 4–395 days). A complete response was documented in four patients while seven patients achieved a partial response.[325]

As a result of the lack of randomised studies in these rare conditions, treatment recommendations are based on expert opinion [C-III].

Chronic disseminated candidosis

Chronic disseminated candidosis (e.g. hepato-splenic candidosis) is not usually a life threatening condition but may often require systemic antifungal therapy for months. After stabilisation of signs and symptoms, chronic disseminated candidosis is not a contraindication for the continuation of antineoplastic chemotherapy or haematopoietic stem cell transplantation in patients with malignancy.[102,326] Two small case series document a continued response in the majority of patients (73% and 87%) with continued systemic antifungal therapy.[327,328]

Data on antifungal treatment in patients with chronic disseminated candidosis are limited to case series with D-AMB with or without flucytosine,[19,328] lipid-formulations of amphotericin B,[329] fluconazole[330,331] and caspofungin.[254] As a result of the need for prolonged antifungal therapy, oral agents such as fluconazole are recommended. The echinocandins or liposomal amphotericin B should be used as initial therapy in unstable patients or refractory patients [B-III]. As a result of the lack of randomised clinical trials, the recommendations on the use of the antifungal agents are based on expert opinion [CIII].

The duration of antifungal therapy in patients with chronic disseminated candidosis should be individualised and may be continued until the resolution of all radiographic signs or calcification of the lesions. By contrast, newer data suggest that hepato-splenic candidosis may represent an immune reconstitution syndrome as concomitant treatment with steroids in addition to antifungals may be associated with rapid resolution of clinical signs.[332] With continuation of chemotherapy or in patients receiving haematopoietic stem cell transplantation, antifungal therapy should be continued[2] [C-III].

Mucocutaneous candidosis

Oropharyngeal and oesophageal candidosis

Uncomplicated oropharyngeal candidosis (OPC) can be treated with topical agents such as polyenes or azoles (B-II),[2,90] systemic (or topical) fluconazole (200–400 mg day^{-1}; p.o. or i.v.) (A-I) or itraconazole solution (A-I), for 7–14 days.[333–337] In OPC cases refractory to fluconazole or in breakthrough infections during prophylaxis with fluconazole, itraconazole (oral solution) (A-II), posaconazole (B-II), anidulafungin, caspofungin, micafungin (B-II) or voriconazole (p.o. or i.v.) (B-II)[338–347] can be used. D-AMB (i.v.) should only be used after failure of the before mentioned therapeutic options[348] (see Table 12).

Oesophageal candidosis should be treated with systemic antifungals (A-II). First choice of therapy is fluconazole (i.v. or p.o.) for 14 to 21 days (A-I). In patients presenting with typical signs and symptoms (OPC together with odynophagia) pre-emptive antifungal therapy may be indicated (B-II).[2,349] Symptomatic improvements are seen within 7 days in most of the patients. Therapeutic alternatives that can also be used in infections refractory to fluconazole are itraconazole (oral solution) (A-I), voriconazole (p.o. or i.v.) (A-I), posaconazole (A-I), anidulafungin (A-I), caspofungin (A-I), micafungin (A-I) or D-AMB (i.v.) (B-II).[50,342,344–347,350–358]

Vulvovaginal candidosis

Most cases of *Candida* vaginitis can be succesfully treated with topical azoles or polyenes. Topical therapy should be applied for more than 7 days. Oral therapy with fluconazole or itraconazole for 1–3 days is an effective alternative[359,360] (A-I). Severe, refractory or relapsed infections may need a prolonged topical treatment, oral fluconazole or itraconazole for more than 14 days, followed by a continous suppressive therapy (B-III).[359,360] Newer antifungals such as voriconazole or echinocandins have not been properly evaluated in this indication. Especially during pregnancy, drugs such as griseofulvin, ketoconazole, voriconazole, flucytosine or potassium iodide are contraindicated.[361] Immunotherapy is not a standard approach to the treatment of genital candidosis.[362]

The treatment of chronic relapsing *Candida* vulvovaginitis is challenging and may not only require antifungal therapy, as psychosomatic factors may be involved.[363]

Candiduria

In patients with urinary catheters, candiduria usually represents colonisation rather than infection and needs no antifungal treatment. Catheter removal alone clears the urine from *Candida* in 40% of the cases, while a change of the catheter leads to a durable sterilisation of the urine in <20% of the patients. A significant benefit of the use of antifungals in patients with colonisation of the urinary tract is not documented.[364,365]

By contrast, in patients with symptomatic candiduria or in granulocytopenic patients, antifungal therapy is recommended (B-III) as is the removal or change of foreign bodies (catheters and stents).[2] If urinary cultures persistently grow *Candida*, an ultrasound should be performed to exclude renal infection (B-III). Systemic antifungal therapy using fluconazole (≥7 days) or D-AMB (≤7 days) has been shown to be effective (B-II).[2] As a result of its activity in non-*Candida albicans* yeast and high concentrations in urine, flucytosine is recommended as part of a combination therapy especially in complicated infections or infections due to non-*Candida albicans* yeast (B-III).[366] Bladder irrigation with D-AMB (50–200 μg ml^{-1}) is an inferior option in most cases and is limited by local toxicity (C-III).[2] In infections due to non-*Candida albicans* yeast, caspofungin or micafungin may be used[367,368] (C-III). Data on the use of anidulafungin or voriconazole in urinary tract infections are lacking. The role of echinocandins in the treatment of candiduria has not been properly studied (C-III).

Candida infections of the skin and nails

Skin infections due to *Candida* are treated with topical azoles or polyenes (A-II). In severe or refractory cases, oral azoles such as fluconazole or itraconazole are

Table 12 Treatment for mucocutaneous infections in adults.

Disease	Drug	Dosage	Evidence	Comment
Oropharyngeal candidosis	Amphotericin B (oral suspension/tablets)	0.5 (to 2.4) g day^{-1}	BI AI	Drug–drug interactions
	Nystatin (oral suspension)	6 × 100.000 I.E day^{-1}	AI	
	Fluconazole	50–200 mg day^{-1}	AI	
	Itraconazole (oral solution)	100–200 mg day^{-1}	AI	
	Posaconazole	100 mg day^{-1}		
Laryngitis	As for oropharyngeal			No data
Oesophagitis	Fluconazole	200–400 mg day^{-1}	AI	Selection of resistant organisms with fluconazole/itraconazole
	Itraconazole (oral solution)	2 × 200 mg day^{-1}	AI	
	D-AMB (i.v.)	0.5–0.7 mg kg^{-1} day^{-1}	CII	
	L-AMB (i.v.)	1–3 mg kg^{-1} day^{-1}	AI	
	Anidulafungin	100 mg day^{-1}	AI	
	Caspofungin	50 mg day^{-1}	AI	
	Micafungin	150 mg day^{-1}	AI	
	Voriconazole	400 mg day^{-1}	AI	
Vaginal candidosis	Clotrimazole (suppository)	Topic	AII	Frequent relapses in immunocompromised host; *Candida glabrata* in HIV+
	Fluconazole	150 mg day^{-1}	AII	
Skin/nails	Fluconazole	50–200 mg day^{-1}	AII	
	Itraconazole	100–200 mg day^{-1}	AII	
Chronic mucocutaneous candidosis (CMC)	Fluconazole	50–400 mg day^{-1}	BIII	Suppressive therapy frequently needed
	Itraconazole	100–400 mg day^{-1}	BIII	
	Posaconazole	100–400 mg day^{-1}	BIII	

recommended[369] (A-II). Treatment of choice for onychomycosis is itraconazole or fluconazole[99] (A-II). As terbinafine is active *in vitro* against dermatophytes only, and not against *Candida* spp, its use is limited to infections due to dermatophytes.[369]

Chronic mucocutaneous candidosis

Chronic mucocutaneous candidosis is a rare disorder that is characterised by persisting or relapsing *Candida* infections of the skin and mucous membranes. Patients may have congenital immunological disorders or endocrine abnormalities. In most of the patients, the syndrome manifests early in infancy. Underlying mechanisms may include disturbances in the activation of T-lymphocytes.[370] In addition, newer data report on disturbances in the signal transduction after human cells encounter yeast as a potential underlying mechanism as documented by mutations in the CARD-9 gene and the Dectin-1-Receptor in some patients with chronic mucocutaneous candidosis.[371–373] As the underlying defects are not treatable, patients typically receive continous or intermittant antifungal therapy with an azole such as fluconazole, itraconazole, voriconazole or posaconazole.[2] Case reports document the usefulness of caspofungin or micafungin in selected cases.[374,375] As a result of a lack of randomised controlled trials, the optimal agent is not defined.

The recommendations are summarised in Table 12.

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