



# Global guideline for the diagnosis and management of candidiasis: an initiative of the ECMM in cooperation with ISHAM and ASM

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*Candida* species are the predominant cause of fungal infections in patients treated in hospital, contributing substantially to morbidity and mortality. Candidaemia and other forms of invasive candidiasis primarily affect patients who are immunocompromised or critically ill. In contrast, mucocutaneous forms of candidiasis, such as oral thrush and vulvovaginal candidiasis, can occur in otherwise healthy individuals. Although mucocutaneous candidiasis is generally not life-threatening, it can cause considerable discomfort, recurrent infections, and complications, particularly in patients with underlying conditions such as diabetes or in those taking immunosuppressive therapies. The rise of difficult-to-treat *Candida* infections is driven by new host factors and antifungal resistance. Pathogens, such as *Candida auris* (*Candidozyma auris*) and fluconazole-resistant *Candida parapsilosis*, pose serious global health risks. Recent taxonomic revisions have reclassified several *Candida* spp, potentially causing confusion in clinical practice. Current management guidelines are limited in scope, with poor coverage of emerging pathogens and new treatment options. In this Review, we provide updated recommendations for managing *Candida* infections, with detailed evidence summaries available in the appendix.

## Introduction

*Candida* species are the predominant cause of fungal infections in patients treated at hospital, causing morbidity and mortality worldwide,<sup>1,2</sup> with both invasive and non-invasive forms of infection occurring in diverse patient populations. Invasive candidiasis and candidaemia typically occur in patients with one or more predisposing conditions, including in those who are immunocompromised or critically ill, whereas mucocutaneous candidiasis can affect otherwise healthy individuals. An increasing number of patients have difficult-to-treat invasive candidiasis due to new, underlying host factors or antifungal resistance, causing increasing health-care use, economic burden, and mortality. Furthermore, the emergence of pathogens, such as *Candida auris* (*Candidozyma auris*), and fluconazole-resistant *Candida parapsilosis*, poses a substantial global health threat, particularly in hospital environments where transmission is easily facilitated. These infections further complicate treatment due to reduced susceptibility to conventional antifungal therapies.

*Candida* comprises a taxonomically unresolved polyphyletic group of only distantly related species.

With new taxonomic studies, several medically important species commonly referred to as *Candida* spp have been taxonomically reclassified (for an overview of these newly proposed changes, please see the appendix p 13).<sup>3</sup> Throughout this Review, both the traditional and revised nomenclature are applied.<sup>3,4</sup>

Timely guidance for the best management approach for mucocutaneous and invasive *Candida* infections is needed. Current international recommendations derive from the Infectious Diseases Society of America and European Society of Clinical Microbiology and Infectious Diseases guidelines, and their respective updates.<sup>5–12</sup> These guidelines have their limitations, for example, by not covering emerging pathogens such as *C. auris*, and not including recommendations for new diagnostics and recently licensed antifungals.<sup>13,14</sup> The European Confederation for Medical Mycology (ECMM) has worked with the International Society of Human and Animal Mycology (ISHAM), the American Society for Microbiology (ASM), and mycological experts from around the world to set out a global guidance initiative, bringing together all disciplines involved in the diagnosis and treatment of *Candida*

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### Key messages

- *Candida* species are leading fungal pathogens, causing both superficial and invasive infections in patients at risk. The emergence of antifungal-resistant strains such as *Candida auris* (*Candidozyma auris*) increases the global health burden.
- Conventional direct microscopy and culture-based methods are still the mainstay of diagnosis of both superficial and invasive *Candida* infections. Biomarkers and molecular diagnostic techniques are helpful in certain clinical settings but there is a lack of reliable data supporting their use in other situations.
- Echinocandins, including the new drug rezafungin, are the recommended first-line treatment for candidaemia and all forms of invasive candidiasis except for CNS and ocular infections due to their broad activity and safety profile. Alternative treatments include liposomal amphotericin B (combined with flucytosine in certain situations) and fluconazole, although fluconazole resistance must be considered. Ibrexafungerp and oteseconazole now complement the antifungal armamentarium for the treatment of superficial candidiasis.
- Incorporating antifungal stewardship measures into health-care systems is crucial for improving guideline adherence and ensuring appropriate use of antifungals. A multipronged approach involving screening, isolation, and environmental cleaning is essential for controlling outbreaks of *Candida* infections.
- New challenges lie ahead: reporting issues of recently proposed nomenclature changes concern microbiologists and clinicians. Novel antifungals in late-stage clinical development will change clinical practice but pose challenges for clinicians with the limited clinical data currently available for many forms of candidiasis.
- This global guideline aims to improve patient management and outcomes for all forms of candidiasis, but adapting to local contexts based on economic circumstances and antifungal resistance patterns might be needed.

disease to provide best-practice multidisciplinary care for patients.

In this Review, recommendations for the management of some forms of candidiasis are summarised. A detailed description of the guideline methodology, evidence summaries, and tables that support each recommendation can be found in the appendix. Additionally, evidence and recommendations for other forms of invasive and mucocutaneous candidiasis, as well as invasive candidiasis in children, adolescents, and neonates can be found in the appendix.

### Guideline development

After the selection and invitation of potential contributors in February, 2020, guideline contributors and

coordinators were defined. To tackle the issue of including contributors from different time zones, recurring videoconferences on methodology were convened. Among the contributors, documents were exchanged via a password-protected OneDrive repository (Microsoft Corp, Redmond, WA, USA) and centrally managed under the oversight of OAC and RS. Population, intervention, comparison, and outcome (PICO) tables were initially filled with all relevant literature from the literature search (see appendix pp 17–18 for search strategy) and suggestions were proposed for quality of evidence and strength of recommendation. Following spellchecking and formatting, the tables' content were discussed. When consensus was reached, the table was labelled as final. If consensus could not be reached, a majority vote was used. Once all tables were finalised, a writing group drafted the first manuscript version and flow charts based on the PICO tables. The draft was circulated to all authors in September and October, 2023, and revised accordingly. Thereafter, a public consultation was conducted using the online survey software EFS Fall 2022 (TIVIAN, Cologne, Germany) from February to April, 2024. The comments and suggestions received were carefully evaluated, and modifications were made as appropriate. The changes were approved in a final review by the authors in August, 2024. 73 scientific societies (including 66 national societies and seven international societies) reviewed and approved the guideline. For further information on methodology, grading system and endorsing societies, please see the appendix (pp 13–20).

### Epidemiology

*Candida* spp are the predominant fungal pathogens, causing fungal diseases in a wide range of patients. Although compromised immunity is associated with an increased risk of developing systemic fungal infections, many patients affected by invasive candidiasis do not have a defined underlying immunodeficiency.<sup>15</sup> Additionally, new targeted biologics, such as IL-17 inhibitors, predispose for *Candida* infections.<sup>16,17</sup> *Candida* spp are responsible for a wide variety of diseases, ranging from superficial—such as cutaneous or mucocutaneous candidiasis, commonly characterised by rash associated with itching and swelling—to life-threatening, systemic candidiasis and candidaemia. Mucocutaneous forms, including oropharyngeal candidiasis and oesophageal candidiasis, are frequently observed in patients with impaired immunity, such as those with advanced HIV disease or uncontrolled diabetes, as well as in people with poor oral hygiene.<sup>18</sup> Oropharyngeal candidiasis is reported as one of the most prevalent opportunistic infections in the advanced HIV disease population (affecting up to 20%), and is often accompanied by oesophageal candidiasis. This association places a considerable number of the estimated 4 million people living with advanced HIV

disease globally at risk.<sup>19,20</sup> In most cases, mucocutaneous candidiasis remains a local infection, but it can also progress to more severe and invasive forms in susceptible individuals.<sup>21</sup>

Latest estimates suggest that over 1 565 000 people are affected by invasive candidiasis every year.<sup>22–24</sup> Candidaemia is the most frequently diagnosed presentation of invasive candidiasis,<sup>25</sup> with most cases being health care-associated.<sup>26</sup> Overall, *Candida* spp account for more than 85% of all cases of fungaemia in Europe and the USA.<sup>26</sup> Vulvovaginal candidiasis is estimated to affect 75% of women at least once during their lives.<sup>27</sup> A nationwide cohort study in Sweden detected an incidence rate of 3·3 per 1000 person-years for the first event of vulvovaginal candidiasis.<sup>28</sup> With about 50% of the women with vulvovaginal candidiasis having at least a second episode, and up to 10% of women potentially having recurrent vulvovaginal episodes per year, the cumulative prevalence is high.<sup>27,29</sup> For detailed information on risk factors, incidence of *Candida* infections, sex differences, and species distribution, including world maps, please see the appendix (pp 21–28).

### Infection prevention and control

Management of scenarios that urge escalation of infection, prevention, and control practices (involving a difficult-to-treat pathogen such as *C. auris*) requires a multipronged, multidisciplinary approach: screening of patients at high risk and close contacts, isolating patients, and performing environmental cleaning are strongly recommended for all inpatient health-care facilities, including hospitals, rehabilitation facilities, and nursing homes. We recommend screening individuals at high risk and close contacts of colonised or infected patients for *C. auris* when they are admitted to inpatient facilities (appendix p 30). Composite swabs of the axilla and groin are recommended to screen for *C. auris*. Specialised, salt-containing media or chromogenic agars should be used for screening by culture, which remains the current primary approach and additionally yields an isolate for susceptibility studies. Recommendations for genomic typing are listed in the appendix (p 30). Close contacts and other patients at high risk can be deisolated after 3 consecutive negative screens taken at least 24 h apart.

Sporicidal and effective hydrogen peroxide, and peracetic acid-based and chlorine-based disinfectants are recommended over quaternary ammonium compounds, which have poor activity against *Candida* spp (appendix p 32).

For an evidence summary of infection, prevention, and control measures, and strategies, please see the appendix (pp 29–32).

## Diagnosis

### Clinical diagnosis

Clinical manifestations of invasive candidiasis include candidaemia, disseminated candidiasis, and single-organ

infection. Detailed analysis of the patient's history and a thorough physical examination, including focused examination of potentially affected organ systems (eg, the cardiovascular system for endocarditis and the neurological system for meningitis), is strongly recommended for all patients with candidaemia, and throughout the course of disease. In haematology patients at high risk with prolonged neutropenia and persistent fever or right-upper quadrant pain, the guideline strongly supports imaging to exclude chronic disseminated candidiasis. For imaging recommendations, please see the appendix (pp 37–41). Physical examination is strongly recommended for diagnosis of mucocutaneous forms of candidiasis, which should be guided by signs and symptoms. For an evidence summary on clinical diagnosis, please see appendix (pp 33–35).

### Conventional diagnostic methods

Conventional culture-based diagnostic methods are strongly recommended, despite limited sensitivity. For adults, two to three blood culture sets with each 20 mL blood volume should be collected when investigating potential candidaemia. The diagnostic yield of blood cultures increases with the collected volume of blood and numbers of bottles incubated. To increase the diagnostic yield of tissue or fluid, direct microscopy should be performed in addition to fungal culture (appendix pp 49–52). For a summary of the evidence on conventional diagnostic methods, please see the appendix (pp 36–37).

### Molecular techniques

Currently, no molecular technique is strongly recommended for any patient population or sample type in diagnosing invasive candidiasis, as pathogen detection is restricted to a limited number of *Candida* spp, and its position in routine clinical use is unclear. Commercial assays have undergone more extensive analytical and clinical validation, whereas in-house methods have limited supporting validation. Therefore, the use of commercial assays is preferred over in-house assays. However, the combined use of molecular-based tools and various biomarkers is moderately supported. *Candida* PCR testing has been focused on blood samples, with panfungal PCR and other broad-range PCR methods being generally used to test invasive samples (eg, cerebrospinal fluid or tissue). Excepting the potentially limited range of species differentiation, the use of molecular tests for the identification of *Candida* spp is moderately supported, particularly in the absence of established alternative methods (eg, matrix-assisted laser desorption ionisation-time of flight [MALDI-TOF] mass spectrometry) or when rapid identification of potentially problematic species (eg, *C. auris*) is needed. For supporting evidence, including evidence tables on molecular techniques, please see the appendix (pp 41–45).

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### Species identification

Identification of *Candida* to the species level is strongly recommended if treatment is being considered, to guide empirical management, to detect outbreaks, and for surveillance. Algorithms incorporating clinical risk have been devised as a guide for identifying when yeast cultured from different specimen types is recommended. Chromogenic agars are strongly recommended for the detection of mixed yeast infections, which occur particularly in patients after solid organ transplantation and surgery. Chromogenic media are moderately recommended for presumptive identification. Biochemical methods are recommended with moderate strength for species identification in settings where MALDI-TOF mass spectrometry or sequencing are not available. PCR assays directly from blood are recommended with moderate strength, given these assays only detect some *Candida* spp, and use of peptide nucleic acid fluorescence in-situ hybridisation (FISH) is recommended with marginal support, primarily because commercial kits are currently unavailable. Molecular identification of culture isolates by MALDI-TOF mass spectrometry is strongly recommended to provide species-level identification. Sequencing from culture isolates is strongly recommended, particularly in specialised labs and when identification could not be obtained by biochemical methods or MALDI-TOF mass spectrometry. For supporting evidence and further recommendations, please see the appendix (pp 45–49).

### Direct microscopy and histopathology

To differentiate between colonisation of skin and mucous membranes, and tissue invasion, a typical inflammatory reaction depending on the host's immune status and the presence of pseudohyphae or hyphae must be shown together with yeast cells for *C. albicans*. However, histopathology does not allow for species identification, and other species, such as *Candida glabrata* (*Nakaseomyces glabratus*), do not produce filaments. Enhancing visualisation of *Candida* elements with optical brighteners in direct microscopy, and applying periodic acid–Schiff or Grocott's methenamine silver staining on formalin fixed paraffin embedded tissue sections are strongly recommended. All forms of *Candida* elements—ie, spores, pseudohyphae, and hyphae—might, in many instances, not be accurately differentiated from several other fungi that contain similar forms. Therefore, confirming the diagnosis of candidiasis in tissue by culture, or by using in-situ identification techniques or panfungal PCR followed by sequencing, is strongly recommended. For supporting evidence, please see the appendix (pp 49–52).

### Biomarkers and serology

Serum  $\beta$ -D-glucan (BDG) testing for presumed diagnosis of invasive candidiasis and candidaemia is

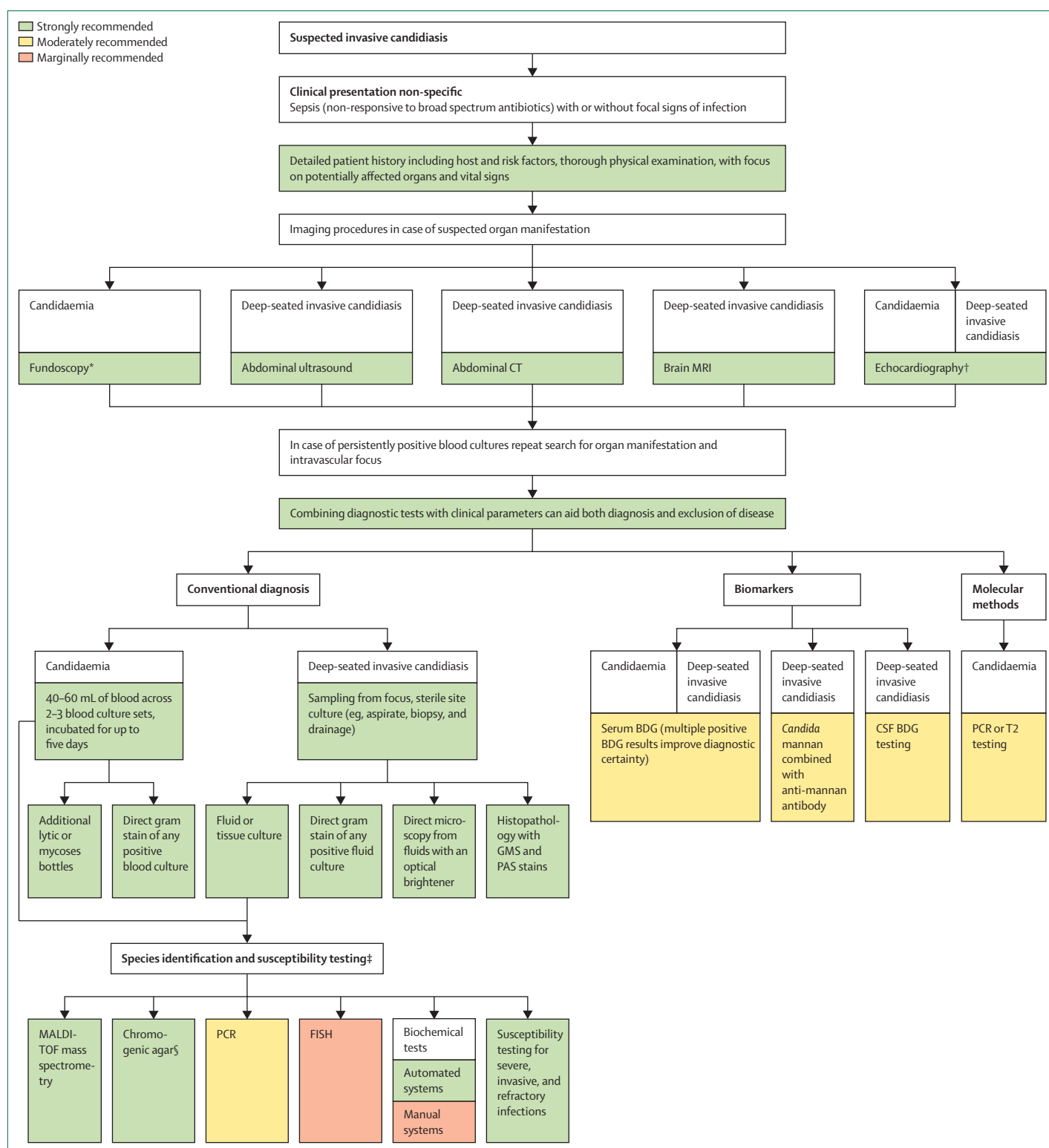
moderately recommended. However, diagnosis of invasive candidiasis or candidaemia should not be solely based on BDG testing, and positive serum BDG alone is not recommended for initiating antifungal treatment in most populations. Results from consecutive serum BDG testing can be used as a tool for treatment stratification. False-positive BDG test results due to factors other than fungal infections, or positive results due to non-*Candida* fungal infections need to be considered. Additionally, although the sensitivity of BDG tests is highly variable between studies, some studies suggest a relevant proportion of false-negative results. This potential error should be considered if BDG is used as a tool for discontinuing antifungal treatment (appendix pp 92–93).

The combination of serum mannan antigen and anti-mannan antibody assays is moderately recommended as an additional tool for diagnosis of candidaemia and invasive candidiasis. Anti-*Candida albicans* germ tube antibodies are marginally recommended for diagnosis of invasive candidiasis caused by *C. albicans*. In suspected CNS *Candida* infection, BDG testing from cerebrospinal fluid is moderately recommended. Detection of mannan antigen from cerebrospinal fluid is marginally recommended for this purpose.

The use of biomarkers for candidaemia or invasive candidiasis only in conjunction with clinical parameters, other biomarkers, or other diagnostic tools is strongly recommended. For details on available evidence, please see the appendix (pp 53–57).

### Susceptibility testing

The use of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical & Laboratory Standards Institute (CLSI) antifungal susceptibility testing for guiding treatment in candidiasis is strongly recommended in all invasive infections, and in mucocutaneous infections that are not responsive to therapy. Robust reference methods with associated epidemiological cutoff values for wild-type versus non-wild-type differentiation and clinical breakpoints for susceptibility classification have been developed; and the data suggest a relevant correlation between minimal inhibitory concentrations and clinical outcome, as well as a correlation between minimal inhibitory concentrations and the presence of resistance mutations in target genes associated with clinical failures. The use of commercial tests is a valid alternative, provided that in-house validation has been performed and supports essential agreement with the reference method from which the clinical breakpoints are adopted. For *C. auris*, the Centers of Disease Control and Prevention (CDC) has defined tentative breakpoints to guide interpretation of CLSI broth microdilution results. Susceptibility testing for attaining epidemiological data is also strongly recommended. The evidence upon which the global guideline recommendations are based, and EUCAST,



**Figure 1: Optimal diagnostic pathway for the diagnosis of candidaemia and invasive candidiasis in adults**

BDG=β-D-glucan. CSF=cerebrospinal fluid. FISH=fluorescence in-situ hybridisation. GMS=Grocott-Gömöri methenamine silver. MALDI-TOF=matrix-assisted laser desorption-time of flight.

PAS=periodic acid-Schiff. \*For patients with ocular symptoms, persistent candidaemia, immunosuppression, and those who are not able to verbalise complaints. †For patients with suspected endocarditis (including clinical signs such as skin lesions or new murmur), persistent candidaemia, presence of valve disease, and those with a cardiac implantable device. ‡Not all methods can identify every species of *Candida*. §For preliminary identification in mixed infection; confirmation needed by another method.

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CLSI, and CDC references are provided in the appendix (pp 57–62).

### Further diagnostic evaluations

Evidence summaries and diagnostic recommendation on endocarditis (appendix pp 37–41), *Candida* CNS infection (appendix pp 62–65), ocular candidiasis (appendix pp 65–68), and chronic disseminated candidiasis (appendix pp 68–69), are provided in the appendix. A graphic illustration of the diagnostic approaches is provided in figure 1.

## Treatment

### Infection specialist consultation

Routine infectious diseases or clinical microbiology consultation for all patients with candidaemia or invasive candidiasis is strongly recommended. If no infectious diseases or clinical microbiology physician is available, antifungal stewardship teams can increase adherence to guidelines (appendix p 72).

### Antifungal stewardship

The guideline group recommends including antifungal stewardship as an essential component in antimicrobial stewardship programmes and quality improvement management. Additionally, we advocate for the establishment of national or international excellence centres that can provide professional advice (appendix pp 73–74).

### Prophylaxis in patients undergoing abdominal surgery

In patients with recent abdominal surgery and recurrent gastrointestinal perforations or anastomotic leakages, fluconazole prophylaxis with a 12 mg/kg loading dose followed by 6 mg/kg once a day is recommended with moderate strength. If patients in the same population were recently exposed to azoles, or if the local hospital epidemiology is dominated by azole-resistant *Candida* spp infections, echinocandin prophylaxis might be considered. For further information and an evidence summary, please see the appendix (pp 80–81).

### Prophylaxis in patients with neutropenia

Azoles are considered the first choice for primary antifungal prophylaxis for patients receiving intensive remission-induction chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome. Because of the shift in the pattern of invasive fungal disease in this clinical context, due primarily to increasing rates of filamentous fungi as well as increasing incidence of non-*albicans* species of *Candida* that have intrinsic resistance or limited susceptibility to fluconazole, primary antifungal prophylaxis with posaconazole or other mould-active drugs are recommended in patients with expected long-term neutropenia (ie, 7 days or longer) from remission-induction chemotherapy for high-risk myelodysplastic syndrome or acute myeloid leukaemia.

For supporting evidence, please see the appendix (pp 85–86).

### Prophylaxis in patients undergoing allogeneic HSCT

In adult patients undergoing allogeneic haematopoietic stem cell transplant (HSCT) for haematological malignancies, primary antifungal prophylaxis with fluconazole has been shown to provide a survival benefit in the early period (ie, in the first few weeks to months) following transplant, as well as in long-term survival. We therefore strongly recommend fluconazole in adult patients undergoing allogeneic HSCT. Fluconazole remains the standard of care in many health-care centres, where it is administered at the initiation of the conditioning regimen through engraftment, and treatment is usually extended to day 75 after HSCT to cover the period of highest risk for the development of acute graft versus host disease.

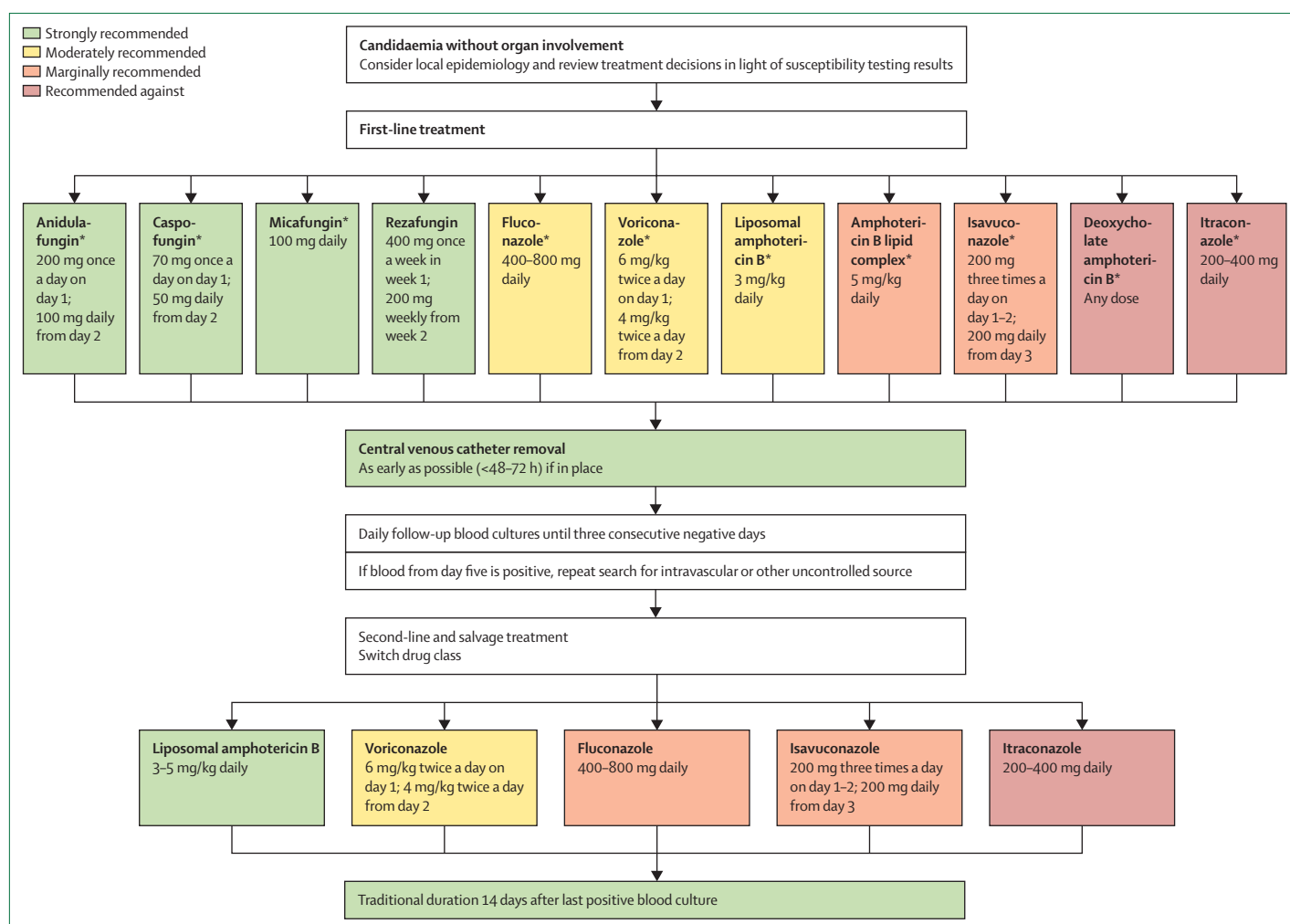
Subsequent trials comparing agents with a broader antifungal spectrum (eg, itraconazole, micafungin, posaconazole, and voriconazole) to fluconazole have shown no difference in terms of effect on candidiasis but have occasionally shown a trend towards less breakthrough mould disease, and a decreased need to use empirical or targeted antimould treatment. However, no study showing that mould-active prophylaxis results in improved survival in the early period or long-term following transplant has been identified. For detailed evidence and recommendations, see the appendix (pp 86–90).

### Prophylaxis in other patient groups

Evidence summaries and recommendations for other patient groups, including for lung, heart, lung–heart, and liver transplants, can be found in the appendix (pp 82–85). For recipients of other transplants, such as the kidney, pancreas, or small bowel, we refer to the appendix (pp 80–81) and recent literature reviews.<sup>30,31</sup>

### Fever-driven treatment

Broad implementation of a fever-driven treatment strategy for patients treated in hospital, including patients at an intensive care unit with fever as the sole symptom, is not supported by existing evidence and the guideline group recommends against the use of this strategy. The guideline group moderately recommends initiating empirical antifungal treatment for patients with septic shock or patients with deteriorating health with additional risk factors of candidaemia, such as prolonged stay at an intensive care unit, an indwelling vascular catheter, or *Candida* spp colonisation. There are no comparative data to support the use of specific antifungal drugs for empirical fever-driven treatment. Therefore, drug selection should be based on the considerations outlined for first-line treatment of candidaemia. An echinocandin should be used as empirical treatment of patients with septic shock, given the superiority of this class over fluconazole as a primary



**Figure 2: Optimal treatment pathway for candidaemia without organ involvement in adults when all treatment modalities and antifungal drugs are available**

\*After 5 days of first-line treatment, consider switch to oral treatment if all six prerequisites are fulfilled: haemodynamically stable; documented clearance of *Candida* from the bloodstream; non-neutropenic; source control; oral azole tolerated; and susceptibility confirmed. If blood cultures from day 5 are still positive, repeat search for an intravascular or other uncontrolled source.

treatment for candidaemia. For supporting evidence, please see the appendix (pp 90–92).

### Diagnostic-driven and biomarker-driven treatment

There are currently insufficient data to support the use of circulating biomarkers or molecular tests for initiating pre-emptive antifungal treatment. Further studies are needed to define the optimal use of BDG testing combined with clinical prediction rules to guide antifungal treatment. We moderately support the use of BDG testing to discontinue empirical antifungals. For detailed background and supporting evidence, please see the appendix (pp 92–93).

### First-line treatment of candidaemia

Echinocandins, including the new agent rezafungin, have a favourable safety profile, activity against a broad range of *Candida* spp (including *C. auris*), and limited drug–drug interactions, which make them suitable as a first-line

therapy. Anidulafungin, caspofungin, micafungin, and rezafungin are strongly recommended as first-line treatment for candidaemia. The spectrum of activity is considered identical between these agents, making them interchangeable based on susceptibility results. However, the choice of echinocandin should be determined by patient-specific pharmacokinetic considerations (eg, hepatic impairment, high bodyweight, drug–drug interactions, or use of extracorporeal membrane oxygenation), and is often additionally directed by costs and hospital policy. If echinocandins are unavailable, or if the patient is colonised or was previously infected with echinocandin-resistant strains, liposomal amphotericin B (LAmB), fluconazole, and voriconazole are moderately recommended due to concerns over drug-related toxicity and drug–drug interactions. Other amphotericin B formulations are not recommended. In this scenario, increasing antifungal resistance to fluconazole needs to be considered. Use of amphotericin B colloidal dispersion,

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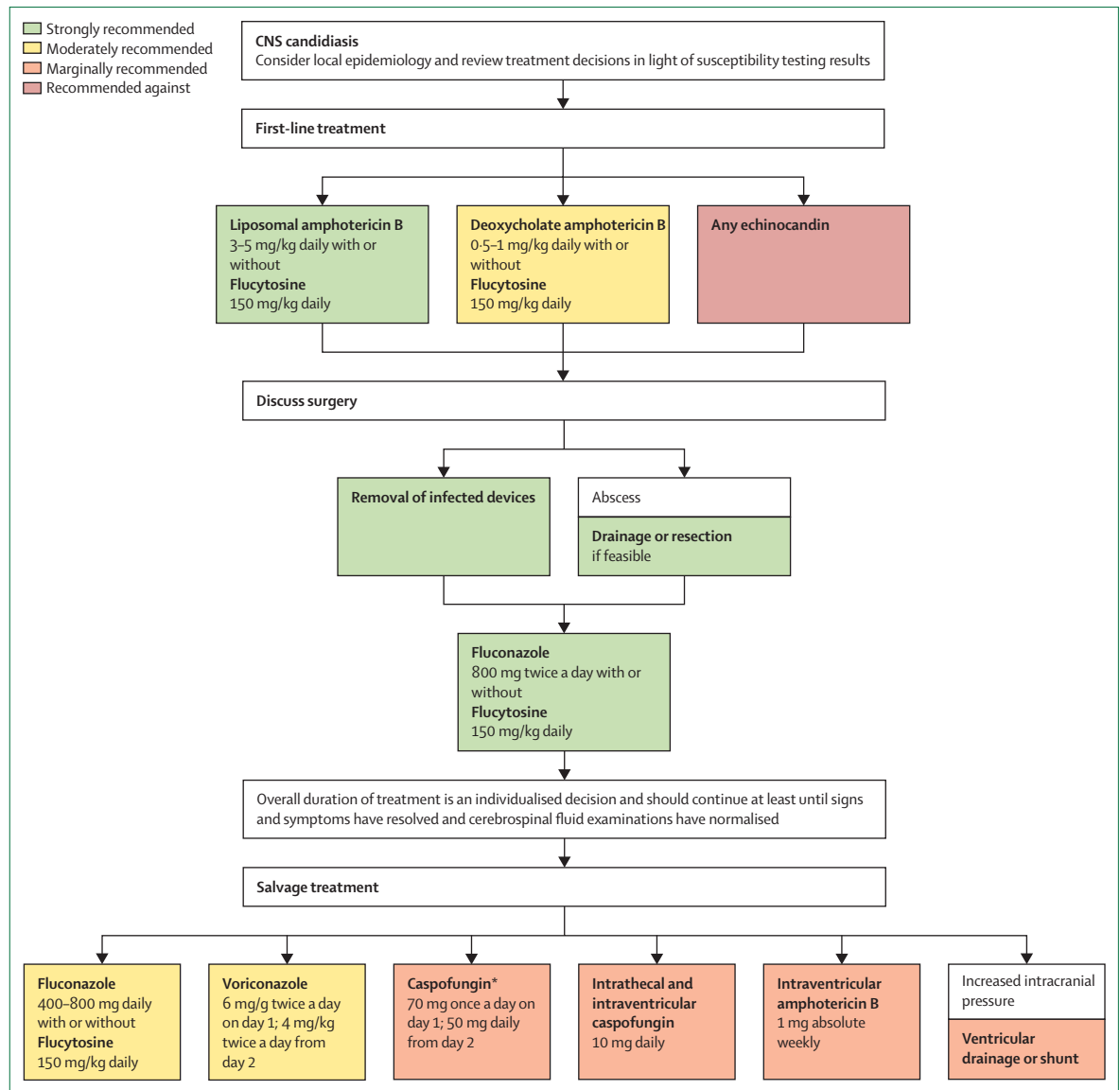


Figure 3: Optimal treatment pathway for CNS candidiasis in adults when all treatment modalities and antifungal drugs are available

\*Echinocandins can be interchangeable, yet published literature only reported use of caspofungin in this setting.

itraconazole, or posaconazole is discouraged whenever alternatives are available. For supporting evidence and further recommendations, please see the appendix (pp 93–99). Figure 2 displays the optimal treatment pathway for candidaemia.

The recommended duration of treatment of candidaemia without deep-seated or metastatic foci is 14 days from the first day of persistently negative blood cultures (ie, three consecutive negative blood cultures). Blood cultures should be performed daily to document the timing of bloodstream clearance of *Candida*. Additional studies are needed to better define the optimal timepoint of blood culture collection for documentation of blood clearance, treatment duration for patients with

candidaemia and various forms of invasive candidiasis, and risk categories for screening echocardiography, fundoscopy, and ultrasound of suspected foci. An evidence summary is given in the appendix (p 100).

### Switch to oral treatment

Switching to an oral azole (fluconazole or voriconazole) is moderately recommended after 5 or more days of echinocandin treatment in patients meeting the following criteria: (1) haemodynamically stable; (2) documented clearance of *Candida* from the bloodstream; (3) non-neutropenic; (4) source control (eg, central venous catheter removal) has been performed; (5) able to tolerate oral azole treatment; and



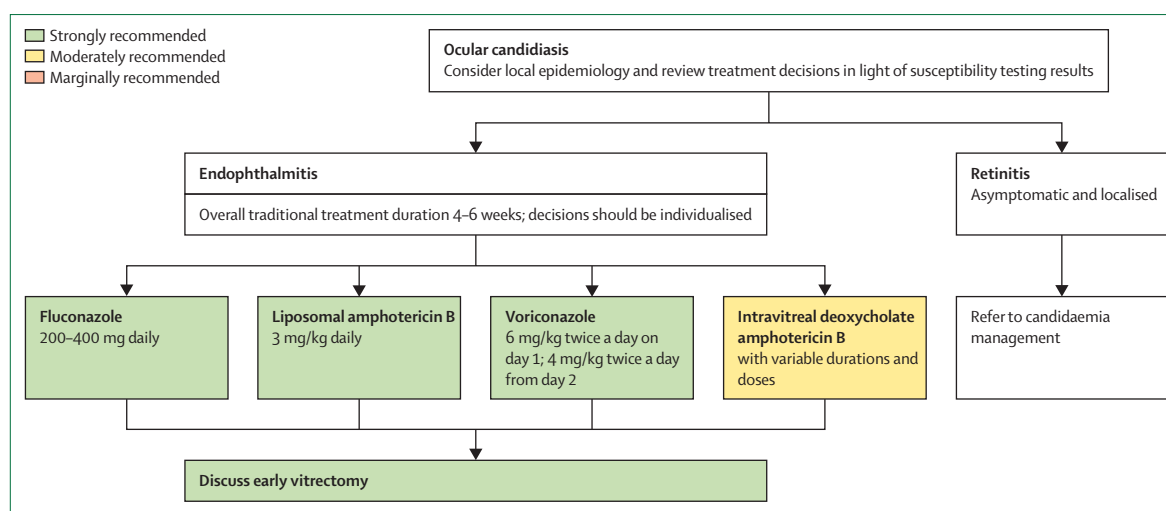


Figure 4: Optimal treatment pathway for ocular candidiasis in adults when all treatment modalities and antifungal drugs are available

(6) susceptibility confirmed to the selected azole. For supporting evidence, please see the appendix (pp 102–103).

### Second-line or salvage treatment of candidaemia

LAmB is strongly recommended as a treatment for candidaemia in patients who cannot be treated with echinocandins due to proven or suspected antifungal drug resistance, treatment failure, or intolerance. Switching to oral fluconazole treatment should be considered as soon as feasible. Fluconazole is only marginally recommended for initial treatment of candidaemia because of concerns arising from high rates of treatment failure and increased antifungal resistance to this drug in some regions. Voriconazole is moderately recommended, but multiple caveats apply, including risk of antifungal drug resistance, drug–drug interactions, and the need for therapeutic monitoring. Knowledge on local epidemiology should be taken into account when choosing second-line treatment as both species distribution (eg, *C glabrata* (*N glabratus*) and *C auris*) and prevalence of acquired azole resistance in *C parapsilosis* differ notably among countries. An evidence summary is provided in the appendix (pp 103–104).

### CNS infection

Based on in-vitro susceptibility, LAmB, usually combined with flucytosine, is strongly recommended for the treatment of CNS candidiasis. Amphotericin deoxycholate is recommended with moderate strength only and should not be used if LAmB is available. Fluconazole, alone or in combination with flucytosine, is strongly recommended as oral consolidation therapy if the *Candida* sp is drug-susceptible. Antifungal therapy should continue until all signs and symptoms of infection have resolved, cerebrospinal fluid examinations have normalised, and imaging evidence of

ongoing infection shows improvement. In patients with suspected infected CNS implants, complete removal of such devices is strongly recommended in combination with intravenous antifungal therapy. For background information and supporting evidence, please see the appendix (pp 104–109). The optimal therapeutic approach for CNS candidiasis is depicted in figure 3.

### Ocular candidiasis

For patients with candidaemia due to azole-susceptible *Candida*, systemic antifungal treatment of ocular candidiasis with fluconazole or voriconazole is recommended. Systemic LAmB formulation is an alternative treatment for ocular candidiasis, particularly when resistance to other antifungal agents is encountered. Given the poor pharmacokinetics of echinocandins within the posterior chamber, these agents are best avoided when treating endophthalmitis. Systemic echinocandins might be considered for patients with asymptomatic and well localised chorioretinitis if candidaemia is caused by echinocandin-susceptible *Candida* spp.

The roles of intravitreal antifungal therapy or vitrectomy, particularly in the management of endophthalmitis, should be evaluated jointly on a case-by-case basis by infectious disease practitioners and ophthalmologists.

The potential severity of *Candida* endophthalmitis justifies 4–6 weeks of systemic antifungal therapy, despite the absence of data on optimal treatment regimens and duration. For patients with *Candida* chorioretinitis and visual symptoms or macular involvement, the guideline group recommends 4–6 weeks of systemic antifungal therapy. For patients with *Candida* chorioretinitis and no visual symptoms or no macular involvement, successful treatment with a systemic antifungal agent for 2 weeks might be sufficient,

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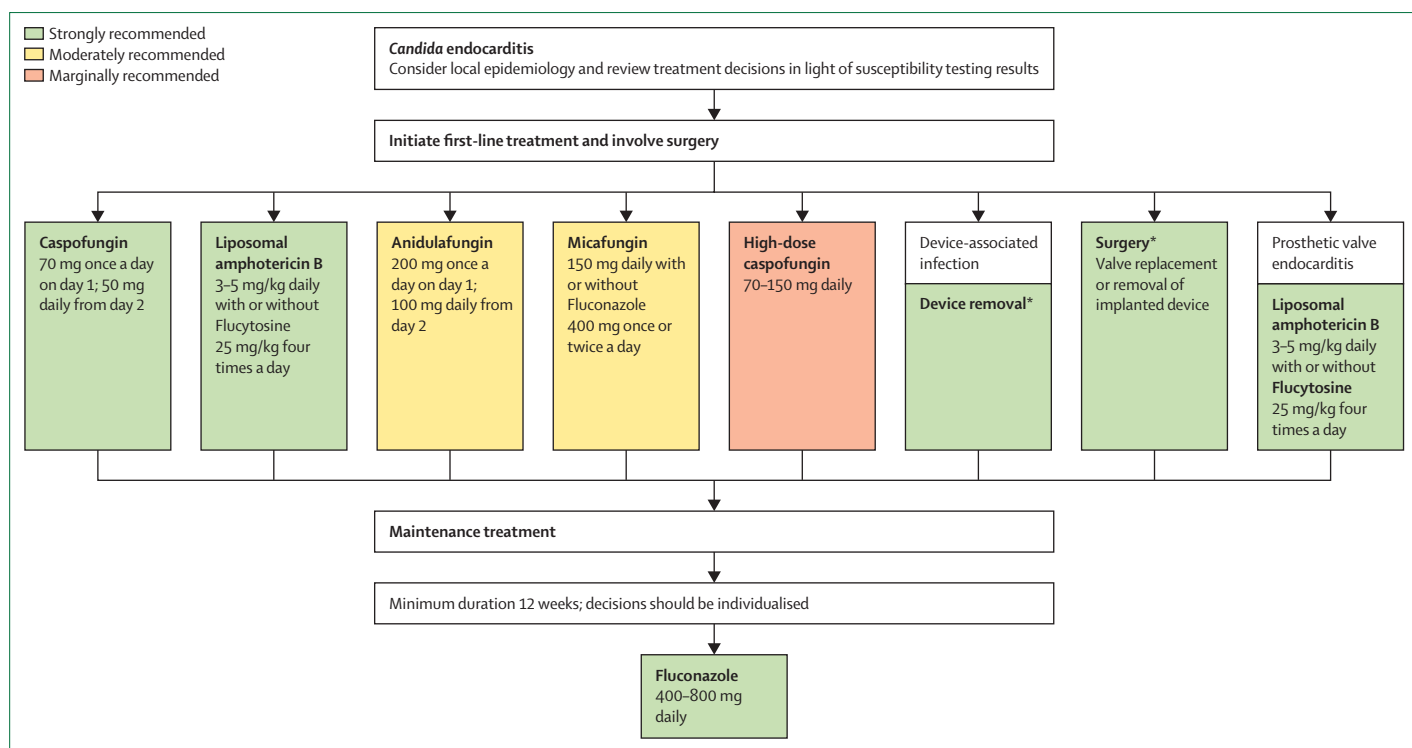


Figure 5: Optimal treatment pathway for *Candida* endocarditis in adults when all treatment modalities and antifungal drugs are available

\*If surgery is not possible or implanted material cannot be removed, consider lifelong suppression with fluconazole (400–800 mg daily).

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if candidaemia has responded clinically to the treatment, and there is no evidence of other sites of deep-seated candidiasis. The role of serial fundoscopic exams in evaluating responses to treatment is not established, but they might be useful in determining treatment duration.

Treatment of *Candida* keratitis involves local application of azoles or polyenes (amphotericin B or natamycin). If systemic antifungal therapy is initiated based on individual considerations, an azole antifungal should be the primary choice. If infection progresses, keratoplasty is the intervention of choice.

For details and supporting evidence, please see the appendix (pp 109–114). The optimal therapeutic approach for ocular candidiasis is depicted in figure 4.

### Endocarditis

Data that compare amphotericin B-based regimens with those based on echinocandins do not indicate with certainty whether either approach confers superior survival benefit. Hence, the guideline group strongly recommends initial therapy either with LAmB (3–5 mg/kg once a day) with or without flucytosine (25 mg/kg four times a day), or with an echinocandin. If substantial renal toxicity develops, the dose can be reduced as necessary, but daily doses below 3 mg/kg are recommended with only marginal strength. Initial therapy with an azole is not recommended. Combined echinocandin–azole or LAmB–echinocandin therapy is

supported with moderate strength. If the isolate is susceptible and other prerequisites are met (appendix pp 102–103), switching to oral therapy with fluconazole (400–800 mg once a day) can be performed. Valvular surgery is strongly recommended for valvular endocarditis within the first week following diagnosis, or earlier. In patients with pacemakers or implantable defibrillators or assist devices, removal of the device is required and strongly recommended.

The guideline committee strongly recommends a duration of therapy of at least 6 weeks after surgery and longer if there are complications (eg, a paravalvular abscess). Longer courses are required when surgery is not possible.

For an evidence summary, please see the appendix (pp 114–118). The optimal therapeutic approach for *Candida* endocarditis is depicted in figure 5.

### Other forms of invasive candidiasis

A summary of evidence and recommendations for treatment of other forms of invasive candidiasis is provided in the appendix, including abdominal candidiasis (appendix pp 118–122), chronic disseminated candidiasis (appendix pp 122–126), bone and joint infections (appendix pp 126–136), urinary tract infections (appendix pp 136–138), *Candida* pneumonia (appendix pp 138–139), and *Candida* empyema thoracis (appendix p 139).

## Source control

Central venous catheter removal in patients with candidaemia is strongly recommended as early as possible when catheter removal can be performed safely. The guideline group strongly supports a recommendation to control the source in patients with invasive abdominal candidiasis and other forms of invasive candidiasis, with or without candidaemia. More studies are needed to define subsets of patients who would benefit from surgical or percutaneous drainage. Detailed evidence and recommendations are given in the appendix (pp 101–102; pp 140–41).

## Mucocutaneous candidiasis

A summary of evidence and recommendations for treatment of oropharyngeal candidiasis (appendix pp 141–43), oesophageal candidiasis (appendix pp 143–44) and vulvovaginal candidiasis (appendix pp 144–47) are provided in the appendix.

## Therapeutic drug monitoring

Access to antifungal therapeutic drug monitoring is highly variable. Where available, therapeutic drug monitoring-guided dosing should be considered for triazoles and for echinocandins in patient populations at risk of extremely low or high drug exposures (eg, premature neonates; patients who are critically ill with an altered volume of distribution or extracorporeal circuits; patients with altered protein binding [eg, severe hypoalbuminaemia]; patients with gastrointestinal absorption issues; expected drug–drug interactions; and morbidly obese patients). Details on patient populations and strength of recommendations for the different triazoles can be found in the appendix (pp 148–49). Additionally, therapeutic drug monitoring can provide useful information in patients with treatment failure. Therapeutic drug monitoring-guided dosing of the echinocandins anidulafungin, caspofungin, and micafungin is less well established, but a target trough of C<sub>min</sub> greater than 1 mg/L is considered to provide acceptable exposure based on current minimum inhibitory concentration distributions and limited clinical data.

For supporting evidence and recommendations for the use of therapeutic drug monitoring in different adult patient populations, please see the appendix (pp 148–49).

## Invasive candidiasis in children, adolescents, and neonates

The paediatric section in the appendix addresses general management considerations for invasive candidiasis, specifically populations at risk, diagnostics, antifungal agent dosing, and recommendations for prophylaxis and treatment of invasive candidiasis in neonates, children, and adolescents. Please see the appendix (pp 150–63) for recommendations and supporting information.

## Dosing recommendations

For an evidence summary and recommendations on pharmacokinetics, dosing, and drug exposure across various adult patient populations, please see the appendix (pp 74–78). For dosing recommendations specifically for paediatric patients, please see the appendix (pp 151–55).

## Conclusion

The current guideline derives from the ECMM's One World—One Guideline initiative,<sup>32–36</sup> in cooperation with ISHAM and ASM, and multiple supporting societies. We sought to engage experts from as many UN-defined world regions as possible to develop global guidance on candidiasis that is stratified for high-resource and low-resource countries, and therefore applicable worldwide. We offer strategies for the diagnostic and therapeutic management of *Candida* diseases. These guidelines can serve as a starting point, but the management options provided need to be tailored to individual health-care settings and patients. For more information on the unmet needs in candidiasis management and future research questions, please see the appendix (pp 164–65).

## Contributors

OAC and RS coordinated the work of the authors and guided the development of the guideline. OAC, RS, MB, SC-AC, AHG, OK, CL-F, LO-Z, RR-R, GR, MES, PLW, AA-I, MCA, JB, AB, RB-A, AJB, JHG, FH, BH, MH, SH, KJ, HEJ, SSK, PK, TL, REL, JFM, MHN, ZDP, P-MR, DS, TT, DCV, and L-PZ wrote the initial manuscript draft. All authors contributed to the literature review, compilation of data, and interpretation and assessment of recommendations. All authors participated in the review and revisions, approved the final manuscript, and are accountable for all aspects of the work and for ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

## Declaration of interests

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See Online for appendix

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