Review

Diagnosis and Treatment of Invasive Candidiasis

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Abstract: Candida species, belonging to commensal microbial communities in humans, cause opportunistic infections in individuals with impaired immunity. Pathogens encountered in more than 90% cases of invasive candidiasis include C. albicans, C. glabrata, C. krusei, C. tropicalis, and C. parapsilosis. The most frequently diagnosed invasive infection is candidemia. About 50% of candidemia cases result in deep-seated infection due to hematogenous spread. The sensitivity of blood cultures in autopsy-proven invasive candidiasis ranges from 21% to 71%. Non-cultural methods (beta-D-glucan, T2Candida assays), especially beta-D-glucan in combination with procalcitonin, appear promising in the exclusion of invasive candidiasis with high sensitivity (98%) and negative predictive value (95%). There is currently a clear deficiency in approved sensitive and precise diagnostic techniques. Omics technologies seem promising, though require further development and study. Therapeutic options for invasive candidiasis are generally limited to four classes of systemic antifungals (polyenes, antimetabolite 5-fluorocytosine, azoles, echinocandins) with the two latter being highly effective and well-tolerated and hence the most widely used. Principles and methods of treatment are discussed in this review. The emergence of pan-drug-resistant C. auris strains indicates an insufficient choice of available medications. Further surveillance, alongside the development of diagnostic and therapeutic methods, is essential.

Keywords: Candida; diagnostic tests; beta-D-glucan; T2Candida; mannan; procalcitonin; echinocandins; azoles; flucytosine; amphotericin B

1. Introduction

Candida species are yeasts and members of the commensal microbial community in humans [1–3]. They are present on skin and mucous membranes of the oral cavity and gastrointestinal and genitourinary tracts [1,2,4–9]. These fungi cause superficial or invasive infections in individuals with impaired immunity [10–12]. The term invasive candidiasis refers to candidemia and infections of other normally sterile sites [13–17].

Risk factors for invasive Candida infections relate to a wide variety of conditions (hematologic and solid organ malignancies, burns, major surgery) and treatment methods (stem cell and organ transplantation, use of immunosuppressive agents, antibiotics, chemotherapy, hemodialysis, intravenous nutrition) [15–22]. Prolonged hospital stay and admission to intensive care units are also recognized as major risk factors for invasive candidiasis [23–25].

The genus Candida includes numerous species [16,26–29]. The most common species to form normal microbiota and potentially cause invasive infections are C. albicans, C. glabrata, C. krusei, C. tropicalis, and C. parapsilosis. These five species are responsible for more than 90% of invasive infections [16,30–33]. Other Candida spp. have also been reported worldwide as causative agents of invasive candidiasis in patients, but to a lesser extent [16]. A novel Candida species—C. auris—has recently emerged as an etiologic agent of invasive candidiasis worldwide [34,35]. The fungus first identified in 2009 in Japan was later found on all continents except Antarctica [36–38]. This species is closely related to the C. haemulonii complex and has five geographically and genetically distant clades [39,40]. The rise in cases
occurred simultaneously in different regions [41,42]. C. auris easily forms biofilms, persist on different surfaces [37,43,44], and has high potential for nosocomial transmission [45,46].

Candidemia, an infection of the bloodstream with Candida spp., is the most frequently detected type of invasive candidia infection. It is the fourth leading cause of nosocomial bloodstream infections in the United States of America (USA) and the seventh in Europe [47]. The overall mortality rate of candidemia is 22–75% [48]. Attributable mortality is rarely estimated due to contributing severe underlying conditions, and ranges from 10% to 47% [27,49]. The prevalence of candidemia differs in various geographical regions, with 0.32/1000 admissions in South-Eastern China and up to 2.49/1000 admissions in Brazil [48]. The distribution of certain Candida spp. as the cause of invasive infections may depend on the underlying conditions and antifungal preparations used. C. glabrata is more likely to be isolated in patients with malignancy and transplantation, and C. krusei in patients with haematologic malignancies receiving fluconazole as prophylaxis [23].

The aim of the present study was to evaluate the diagnostic and treatment options for the management of invasive candidiasis.

2. Diagnosis of Invasive Candidiasis

2.1. Clinical Manifestations of Invasive Candidiasis

Clinical manifestations of invasive candidiasis are generally non-specific [50,51]. The few exceptions are specific lesions in chronic disseminated candidiasis (CDC) and ocular candidiasis. CDC is a form of invasive fungal infection affecting the liver, spleen and, rarely, other organs. It occurs most commonly in patients with acute leukemia treated with chemotherapy. The typical small, target-like abscesses in the liver or spleen, described as “bull’s-eyes”, and detectable on ultrasound, computed tomography or magnetic resonance imaging, accompanied by elevated levels of serum alkaline phosphatase, support diagnosis without additional mycological data. Ocular lesions are visible as progressive retinal exudates or vitreal opacities upon the ophthalmologic examination. Their diagnostic value increases if an episode of candidemia is present within the previous 2 weeks. Candida chorioretinitis or endophthalmitis occur in up to 45% of cases of invasive candidiasis associated with candidemia [52–59].

Other symptoms and signs of invasive candidiasis usually do not differ from infections of another origin [60]. This fact, along with often insufficient laboratory data, contributes to the complexity of differential diagnosis and leads to the introduction of the terms of possible, probable and proven invasive candidiasis [59,61–63]. These definitions are intended for epidemiological studies and the evaluation of diagnostic tests and antifungals, but not to guide individual patients’ care [59,63]. According to the last update of the regularly revised consensus on the diagnosis of invasive fungal infections, the definition of probable invasive candidiasis is based on the assessment of host factors, clinical manifestations, and mycological non-cultural evidence, while the term possible infection in connection with invasive candidiasis is no longer defined [59,61]. Proven invasive candidiasis usually requires confirmation with “gold standard” methods.

2.2. “Gold Standard” Methods for the Diagnosis of Invasive Candidiasis

The “gold standard” for the diagnosis of invasive candidiasis has long been positive cultures or, alternatively, histopathology from normally sterile sites [49,64,65]. The last consensus guidelines on the diagnosis of invasive fungal infections introduced four possibilities to prove the diagnosis of invasive candidiasis. First, histopathologic, cytopathologic, or the direct microscopic detection of Candida pseudo- or true hyphae in specimens from normally sterile sites obtained by needle aspiration or biopsy. Second, positive culture from a sample obtained by a sterile procedure from a normally sterile site with clinical or radiological abnormality consistent with infection. This point includes samples from freshly placed drains (within 24 h). Third, the detection of Candida species by polymerase chain reaction (PCR) with subsequent DNA sequencing if yeasts are found microscopically in paraffin-embedded tissue. Fourth, blood culture positive for Candida species [59].
Candidemia, as the most frequently diagnosed invasive infection, results in deep-seated candidiasis in about 50% of cases due to hematogenous dissemination [66]. Cultures of *Candida* spp. become positive with the concentration of 1 CFU/mL, demonstrating high efficacy in discovering viable *Candida* cells [67]. The easiest test to diagnose invasive candidiasis is the blood culture test, though the efficiency of the procedure is low: *Candida* spp. are isolated from blood in only 21–71% of patients with autopsy-proven invasive candidiasis [68]. The sensitivity can be improved with an increase in the volume of the blood sample and the frequency of blood testing. These culture methods retain their importance, and will continue to do so in the years to come, due to the possibility of the isolation, identification and susceptibility testing of the infectious agent [68–70]. The main drawback of culture methods is that they are long, with a 72–96 h turnaround time leading to delays in proper treatment that results in increased mortality [67,71,72]. Another disadvantage is poor performance in neonates with candidemia and concurrent *Candida* meningitis when blood, as well as cerebrospinal fluid cultures, are generally sterile [27]. These facts have led to the rating of positive urine cultures, similar to blood ones, and the use of surrogate tests including thrombocytopenia and elevated C-reactive protein as predictors of candidemia in infants [73,74].

Samples are taken directly from the deep-seated sites of infection culture *Candida* in less than 50% of patients with invasive candidiasis: the possible reasons encountered are low concentration, uneven distribution of viable cells, and the small size of the sample [67]. The diagnostic struggle in deep-seated *Candida* infections is aggravated by invasive techniques required for sampling that are risky or contraindicated to patients with severe underlying conditions [67].

Special stainings, such as the periodic acid–Schiff stain, are capable of detecting polysaccharides and glycoproteins of the fungal cell wall; the Grocott–Gomori methenamine silver stain that targets carbohydrates is also used in histopathology [64,75–79]. The use of stains with fluorescent brighteners can increase sensitivity [27].

### 2.3. Identification of Candida Species

The identification of the etiologic agents of invasive candidiasis is a very important step in diagnostic procedures due to the high diversity of *Candida* species and the intrinsic or acquired resistance typical to selected species [80].

During the Antifungal Surveillance Program of the SENTRY study, which was ongoing for 20 years from 1997 until 2016 in 135 medical centers in 39 countries, 20,788 invasive *Candida* isolates were collected. *C. albicans* was the most prevalent species: it accounted for 46.9% cases, followed by *C. glabrata* and *C. parapsylosis* with 18.7% and 15.9%, respectively. *C. tropicalis* was isolated in 9.3%, *C. krusei* in 2.8%, and miscellaneous *Candida* species in 6.5% of cases of invasive candidiasis (Figure 1) [81].

With the development of the modern taxonomy of microorganisms based on phylogeny, sequencing and Matrix-Assisted Laser Desorption–Ionization Time-Of-Flight (MALDI-TOF) mass spectrometry were introduced into laboratory practice, with the former cornerstone identification methods based on biochemical and physiological properties of different *Candida* species having lost their reliability. Biochemical tests based on chromogenic media still retain their value in diagnostics due to their ability to help differentiate mixed cultures, though they have limited capacity in the identification of uncommon *Candida* spp. [82–86]. Conventional methods show only 15–76% accurate identification [87] and are time consuming [80]. The biochemical methods implicated in automated identification systems cannot be considered reliable either: the VITEK 2 system demonstrates only 15.2% correct identifications of *C. guilliermondii*. This error might seriously mislead the administration of the correct treatment for the patient, since this species has reduced susceptibility to echinocandins due to its *FKS* gene polymorphism [88,89]. The API ID32C biochemical test system misidentifies *C. parapsilosis* and other *Candida* spp., for example, *C. sake*, which could also result in the failure of treatment, as these two species have different resistance patterns *C. sake*, contrary to *C. parapsilosis*, has decreased susceptibility to fluconazole and other triazoles [88]. Con-
Conventional methods often lead to *C. famata* misidentification [87, 88]. *C. auris* is identified with biochemical assays incorrectly in most cases [39, 90, 91].

**Figure 1.** Candida species most frequently isolated in patients with invasive candidiasis during the SENTRY study.

The most reliable method that is currently used for the identification of fungi in routine laboratories is the Sanger sequencing of the ITS region and/or D1-D2 domain [92–94]. However, the ITS region seems to have limitations in differentiating closely related fungal species due to a lack of resolution and the presence of non-homologous copies of ITS in the genome [93]. Sequencing provides precise *Candida* species identification but is time-consuming and requires qualified staff [95–97]. The well-performing molecular method capable of correctly identifying *Candida* spp. is MALDI-TOF mass-spectrometry [98]. The technique is based on the comparison of the generated unique spectral fingerprints of the tested fungus with the database of mass spectra [60]. It provides accuracy, is comparable with sequencing, and is capable of identifying a *Candida* isolate to species level in less than 15 min [98, 99]. This method is cost-effective, does not require expensive reagents or a highly qualified team, and has wide libraries which can be extended in-house [99–101]. The only drawback is the price of the equipment that makes it too expensive for routine laboratories in low-income regions [100, 101].

There are several disadvantages of the diagnostic techniques based on the culture or histopathology of invasive candidiasis, including low sensitivity and the fact that sampling from sterile sites may be harmful to patients at risk of invasive candidiasis due to severe underlying conditions [59, 102]. This information led to the study of *Candida* cultured from non-sterile sites in critically ill patients as an indicator of invasive candidiasis. Earlier studies demonstrated the association of *Candida* isolated from multiple non-sterile sites with candidemia, and further applied genetic techniques with confirmed strong associations of *Candida* strains derived from sterile and non-sterile samples [103–105]. This approach cannot be used to establish the diagnosis of invasive candidiasis, though it may be helpful in some cases without culture-proven infection as it allows the determination of the most probable infectious agent and the antifungal susceptibility testing of alternative isolates from probes other than normally sterile fluids or organs.
2.4. Non-Cultural Laboratory Techniques

The low sensitivity of “gold standard” methods has led to the development of non-cultural and non-histopathological laboratory techniques for the diagnosis of invasive candidiasis.

The first non-cultural diagnostic tools for invasive candidiasis were tests based on *Candida* antigens and anti-*Candida* antibody detection in patients’ serum [67]. Most *Candida* antigens demonstrated low concentrations and were rapidly cleared from the patients’ blood. The cell wall antigens mannann and β-D-glucan appeared to be promising targets [67,106,107]. The first tests to be introduced into practice were immune assays capable of detecting mannann and anti-mannann antibodies. The estimated sensitivity and specificity of both methods used simultaneously did not exceed 55% and 65%, respectively [108]. Interestingly, immunoglobulin G, especially in IgG₂ assays, performed better than immunoglobulin M assays, and was able to suggest previous *Candida* infections in patients [67,109]. A high level of antibodies can be detected in patients with prior *Candida* infection without concurrent invasive candidiasis, especially in cases of autoimmune or other immunocompromised conditions, thus explaining the low positive predictive value of a single antibody detection test. The increase in antibody concentration might be more helpful in the diagnosis of candidiasis, but it requires at least two blood samples taken in two weeks, does not provide the early diagnosis of infection, and is not discriminative enough in the diagnosis of invasive candidiasis. The detection of mannann can be misleading due to the wide distribution of *Candida* spp. in numerous biotopes of the human body. Currently, neither mannann nor anti-mannann antibody detection have been approved for the diagnosis of invasive candidiasis by the US Food and Drug Administration (FDA).

The detection of beta-D-glucan, a cell wall compound of *Candida* spp., is used as a biomarker of invasive fungal infection with a sensitivity of 92% and specificity of 81% for the diagnosis of invasive candidiasis [108,110–115]. The main drawback of this method is the presence of beta-D-glucan in other fungi, including *Aspergillus* spp. and *Pneumocystis jirovecii*, that makes its use unreliable in the diagnosis of infections caused by *Candida* spp. Still, the high negative predictive value of this test is helpful in the exclusion of the diagnosis of invasive candidiasis. The test is approved by the FDA for the diagnosis of invasive fungal infections and is recommended as mycologic evidence for the diagnosis of probable invasive candidiasis (Table 1) [59,115].

| Test                                    | Turnaround Time | Diagnostic Value | Sensitivity | Specificity | Notes                                                                 |
|-----------------------------------------|-----------------|------------------|-------------|-------------|-----------------------------------------------------------------------|
| Culture                                 | 2–4 days        | Positive         | 21–71%      | N/A         | Allows susceptibility testing                                          |
| T2Candida                               | 3–5 h           | Positive         | 91%         | 99%         | Approved for the detection of *C. albicans*, *C. krusei*, *C. tropicalis*, and *C. glabrata* in whole blood. |
| β-D-glucan (Fungitell)                   | 1 h             | ≥80 ng/L         | 92%         | 81%         | Can be positive in other fungal infections                            |
| β-D-glucan + procalcitonin              | 1 h             | ≥80 ng/L         | 96%         | 98%         | Can be positive in other fungal infections                            |

Table 1. Tests approved for the diagnosis of invasive candidiasis.

The *Candida albicans* germ tube antibody test (CAGTA), intended to discriminate between infection and colonization, detects antibodies against antigens of the mycelium of the fungus in human serum or plasma. It demonstrates variable sensitivity (53–74%) and specificity (57–92%) with lower sensitivity for non- *albicans* Candida spp. [108,114,116,117]. The combination of various non-cultural tests—e.g., CAGTA, beta-D-glucan or mannann antigen tests—has a higher negative predictive value than single tests, and has been proved to be useful for decision making to discontinue unnecessary therapy in suspected invasive candidiasis [114]. The combination of two tests, including one of the *Candida* antigen detection methods and procalcitonin, seems to be even more promising in clinical practice.
when the early differential diagnosis of infection is crucial in severely ill patients. Procalcitonin levels in invasive candidiasis do not exceed 2 ng/mL opposite to highly elevated levels in bacterial, especially Gram-negative sepsis. The combination of procalcitonin level <2 ng/mL with the positive β-D-glucan test demonstrates sensitivity of 66% and specificity of 98% for invasive candidiasis [27,115].

PCR provides the identification of Candida spp. in 2–4 h and the possibility of monitoring the infection by indicating persistence or resolution [64]. This method showed high specificity and sensitivity in one trial 92% and 95%, respectively) [64]. PCR-based tests, which are highly effective in the diagnosis of infections caused by pathogenic bacteria or viruses, have lower reliability in the diagnosis of invasive candidiasis. The problem arises from the low number of Candida cells in the blood, often under 1 CFU/mL, and the wide distribution of fungus and its DNA in the human body and the environment, as well as similarity between human and fungal DNA [27,118,119]. Still, further development of PCR tests could increase the rate of detection of invasive candidiasis. There is already a wide variety of commercially available tests with PCRs alone or PCRs with subsequent electrospray ionization mass spectrometry, sequencing, or T2 nuclear magnetic resonance allowing the detection of Candida DNA directly from blood samples [120–124]. The latter, known as T2Candida panel (T2 Biosystems, Lexington, MA, USA), with sensitivity and specificity values of 91.1% and 99.4%, respectively, has been approved by the FDA and included in the list of non-cultural methods suitable for the diagnosis of probable invasive candidiasis and the detection of C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, and C. krusei in whole blood (Table 1) [59,125,126].

Another non-cultural approach to the diagnosis of invasive candidiasis—the detection of Candida metabolites—has long been considered promising. The first metabolite to be used in the diagnosis was D-arabinitol, a metabolite produced by the several most common Candida spp. associated with invasive candidiasis, with the exception of C. krusei and C. glabrata. It can be measured in serum or urine [127]. This approach, however, did not confirm its effectiveness in the diagnosis of invasive candidiasis, and the detection methods were not standardized or validated [127].

With the development of omics technologies—genomics, transcriptomics, proteomics, and metabolomics—new hopes for the more precise diagnosis of invasive candidiasis have emerged. The study of the metabolomes of different Candida spp. seem to be currently the most promising and capable to define candidate compounds for approved diagnostic methods. Several databases of metabolomes of Candida spp. already exist (the YMBD or the Yeast Metabolome Database, the METLIN Metabolite and Chemical Entity Database, the LMISSD or LIPID MAPS In-Silico Structure Database, etc.) [128,129]. The work on the metabolomic profiles of different Candida spp. is currently at the early stage, and their potential for application in diagnostics is to be estimated in the future.

Genomic studies could provide the precise identification of infectious agents and antifungal susceptibility testing directly from a sample or an isolate. These methods are currently widely used in science and need trials to estimate their usefulness in routine practice. The possible implementation is additionally dependent on the decrease in the price of equipment and reagents, as well as the development of standardized procedures. Recent genomic studies in patients have revealed new host factors for invasive candidiasis: the significant association between candidemia and the single-nucleotide polymorphisms (SNPs) in CD58, LCE4A, and TAGAP loci has been demonstrated. The combination of two or more hazardous alleles resulted in a 19.4-fold increase in risk of candidemia [130,131]. The evaluation of host factors for invasive candidiasis with human genomics can improve diagnostics and estimate the patients in need of prophylaxis.

2.5. Antifungal Susceptibility Testing

The antifungal susceptibility of a Candida isolate is a cornerstone for the choice of antimicrobial agent and the treatment of invasive candidiasis. There are two major institutions issuing regularly updated guidelines for antifungal susceptibility testing performance
and analysis: the Clinical and Laboratory Standards Institute (CLSI) and the European Union Committee on Antimicrobial Susceptibility Testing (EUCAST) [132,133]. The latter is easier to follow due to the free data provided. Both institutions issue well-established recommendations for testing performance in fungi, though they have insufficient information on some aspects of antifungal susceptibility analysis. EUCAST currently provides neither information on the assessment of the minimal inhibitory concentrations (MIC) of antifungals for C. guillermondii, nor caspofungin and isavuconazole interpretive guidelines for Candida spp. [133,134]. The emerged C. auris, which is capable to cause outbreaks of bloodstream infections in intensive care units, does not have any guidelines in either system. The only recommendations issued are tentative MIC breakpoints by the US Centers for disease control and prevention that lack information for all azoles except fluconazole and 5-fluorocytosine [135,136]. Another problem has arisen from the recently revealed inaccuracy of the Sensititre YeastOne panels widely used in routine laboratories, which have previously been considered precise tools for studying MIC in a wide variety of antifungal agents against Candida spp., predominantly for the assessment of MIC in echinocandins and fluconazole (i.e., in detecting caspofungin activity against C. krusei and C. glabrata, or fluconazole activity against C. parapsilosis) [137–140]. Vitek 2 can provide falsely high MICs of amphotericin B and caspofungin against C. auris [141–143]. The CLSI or EUCAST reference methods require high qualifications of the staff. As a rule, these tests are performed in reference laboratories, thus leaving patients with delayed answers; this is critical for the right choice of therapy and outcome [138,144,145]. The upgrade in interpretive criteria and the further development of precise and convenient test systems for everyday use could help improve patients’ care.

3. Treatment of Invasive Candidiasis

3.1. Principles of Therapy

The outcomes in patients with invasive candidiasis are generally dependent on mycological cure, the severity of the underlying conditions, and the time frame of therapy. The delay in the introduction of antifungal treatment for each 12–24 h may result in increases in mortality rate of up to 100% [49].

There are three major points that affect the outcome and duration of invasive candidiasis. First is the early diagnosis of infection. This requires the analysis of risk factors and clinical manifestations and the prompt use of all available approved cultural and non-cultural diagnostic methods [27,146]. Second is the search for the possible source of infection and its removal. It is very important to eliminate all blood and urine catheters, often encountered as sources of infection, as well as prosthetic devices where possible. All catheters and devices should be cultured upon removal. The surgical debridement of the site of infection has to be performed or, alternatively, the drainage of abscesses or infected peritoneal or pleural fluids should be performed [21,27,69,126,147]. Third, early effective systemic antifungal therapy has to be administered [69,126]. The delay in the administration of antifungal therapy, inappropriate formulations, and inadequate dosages result in higher mortality rates [148–150]. It is important to consider both the susceptibility of the yeast and drug–drug interactions along with the PK/PD data which have a high impact on certain loci of infections (e.g., in Candida endocarditis, Candida endophthalmitis, the central nervous system, or bone tissue involvement) [27].

The deficiency in reliable and sensitive methods for the diagnosis of invasive candidiasis and the long time (2–4 days) necessary for the isolation of fungus and susceptibility testing makes the early treatment that is crucial for a positive outcome challenging. The major aim is to start therapy as early as possible and use the effective regiment, but this is not easily feasible. There are several regularly updated detailed guidelines for the treatment of invasive candidiasis that can be helpful to healthcare professionals [150,151].
3.2. Antifungal Preparations

Systemic antifungals are used in the treatment of invasive candidiasis. There are four classes of preparations that differ in their mechanisms of action. One of the earliest systemic antifungal preparations introduced to clinical practice in 1959 was polyene amphotericin B [152]. It has been successfully used in the treatment of different invasive fungal infections, including candidiasis, since that time. Polyenes bind to ergosterol, the major component of the fungal cell membrane, creating pores and subsequent cell death [153,154]. These agents have a broad spectrum and a potent fungicidal effect. Most Candida species retain susceptibility to systemic polyenes. However, resistance is frequently detected in C. lusitaniae [155]. Amphotericin B and its lipid formulations are the only systemic polyenes available with lipid formulations less toxic and better tolerated by patients [156]. The use of conventional amphotericin B is limited by often-encountered individual intolerance and nephrotoxicity [157–159].

5-fluorocytosine (flucytosine) was developed as an antimetabolite in 1957. It inhibits fungal protein synthesis after being converted to 5-fluorouracil by cytosine deaminase and incorporated into fungal RNA, replacing uridylic acid. It is also a potent inhibitor of fungal DNA synthesis through the inhibition of thymidylate synthetase [160,161]. The drug is effective against a wide range of Candida spp., is well tolerated, and has a synergistic effect with amphotericin B. Flucytosine is used in combination with amphotericin B in invasive candidiasis in neonates with Candida meningitis due to its superb penetration into the cerebrospinal fluid. The use of flucytosine monotherapy is limited due to easily emerging resistance [162–165]. Hematologic and hepatic toxicities are associated with flucytosine administration. The careful monitoring of blood cell count is recommended. The adjustment of dose is advocated in patients with renal dysfunction: serum concentration monitoring is helpful [164].

Systemic azoles and currently widely used triasoles have several antifungal formulations, including fluconazole, itraconazole, voriconazole, posaconazole, ravuconazole, and isavuconazole. Azoles inhibit lanosterol 14α demethylase, a key enzyme of ergosterol biosynthesis. Azoles generally demonstrate fungistatic activity against Candida spp. Most of them are active against fungi, causing invasive candidiasis with some agents, and demonstrating decreased activity against certain species. Resistance to fluconazole is most common in C. auris, C. glabrata, and C. parapsilosis; C. krusei has intrinsic resistance to fluconazole. Resistance to other azoles is rarely encountered, though increasing in frequency [166–169].

Echinocandins (micafungin, anidulafungin, caspofungin) present the newest class of antifungals and feature a fungicidal effect in Candida species. Their mechanism of action is the inhibition of β-D-glucan synthase: the important enzyme in cell wall synthesis. All echinocandins have high efficiency in invasive infections and an exceptional safety profile. A novel echinocandin rezafungin with once-weekly dosing and activity against Candida spp., including subsets of echinocandin-resistant Candida auris, has been recently developed and is currently in phase III trials [170–176]. Echinocandins demonstrate wide distribution in different organs and tissues, except the brain and eyes [52,177].

3.3. Choice of Antifungal Preparations and Duration of Treatment

Early diagnosis and early efficient initial therapy play a crucial role in the outcome of infection: a 24 h delay in obtaining positive blood cultures is associated with an almost two-fold increase in mortality in cancer patients [178]. Echinocandins are considered the drugs of choice for initial therapy in most cases of invasive candidiasis [179–181], though it depends on the severity of infection, data on the effectiveness of the antifungal treatment in previous episodes and intolerance to antifungals, the involvement of organs that demand specific permeability, and the tissue distribution of the agent (central nervous system, valves, bones, articular tissues, etc). Data on the dominant pathogen and its antifungal susceptibility in certain hospital settings, such as wards and departments, especially in non-neutropenic patients when an exogenous source of infection is suspected, are also important (Table 2).
Table 2. Therapy of invasive candidiasis and preferred medications.

| Etiologic Agent of Invasive Candidiasis Therapy | C. albicans, C. parapsilosis, C. tropicalis | C. krusei, C. glabrata | C. auris |
|-----------------------------------------------|-------------------------------------------|-----------------------|---------|
| First-line therapy *                          | Echinocandin                              | Echinocandin          | Echinocandin |
| Alternative first-line therapy                | Fluconazole                               | Amphotericin B lipid formulations | Amphotericin B lipid formulations |
| Step-down therapy **                         | Fluconazole                               | Voriconazole          | Susceptibility data required |

Notes: * Liposomal amphotericin B and flucytosine are used in the central nervous system or for eye infections. ** Step-down therapy is based on MIC assessment in individual cases.

Echinocandins were effective as initial treatment in 70–75% of patients with invasive candidiasis, according to randomized clinical trials [27,180]. Lower than expected survival rate might be due to the insusceptibility of the fungus to the agent used, or other circumstances (severe underlying condition or infection, delay in diagnosis or the initiation of therapy, non-performed debridement, or poor permeability of the drug into the infected site) [182–186]. An analysis of seven randomized clinical trials in roughly 2000 patients with invasive candidiasis showed that choice of an echinocandin as the initial treatment was associated with a significantly lower 30-day mortality rate compared with azoles or amphotericin B [150]. Worse outcomes were associated with C. tropicalis infections, higher APACHE II score, and older age [150]. C. parapsilosis usually demonstrates higher MIC to echinocandins than other Candida spp. Nevertheless, data from several clinical trials have shown that initial therapy with any echinocandin is appropriate for patients with C. parapsilosis infection, contrary to infections caused by other Candida spp. with acquired resistance to echinocandins [187–189]. Two randomized trials compared an echinocandin with an azole as a first-line therapy of candidaemia. One of them demonstrated that overall response rates were lower with fluconazole (60%) examined against anidulafungin (76%); another provided similar data for isavuconazole (60%) compared with caspofungin (71%) [182].

De-escalation or step-down therapy with changes from echinocandins to azoles provides favorable results in invasive candidiasis with different organ involvement (Table 2). The step-down therapy is normally started after 3–7 days of initial treatment and is administered in accordance with the results of susceptibility testing. Fluconazole could be the perfect choice for infections caused by susceptible strains with high efficiency, well-tolerability, and oral formulations with absorption from the gastrointestinal tract above 90% (Table 2). Several clinical trials did not reveal any differences in the 30-day survival or mycological cure rates of patients who received echinocandin therapy and those who were transferred to de-escalation therapy with oral azoles, according to susceptibility testing after 5 days of treatment with echinocandin [184,190]. Another option for step-down therapy with azoles in invasive candidiasis is voriconazole active against C. guilliermondii, C. glabrata and C. krusei with reduced susceptibility or resistance to fluconazole. De-escalation therapy significantly decreases the financial burden of invasive candidiasis for healthcare systems, with reduced hospital costs and shortened stay, as azoles, unlike echinocandins, can be successfully administered as oral formulations.

Azoles have some advantages compared to echinocandins as a first-line therapy treatment for the involvement of certain organs. Contrary to echinocandins, azoles easily cross the blood–brain barrier, making them the drug of choice for initial treatment in cases with central nervous system involvement. Fluconazole is widely used in low-income countries with a low prevalence of azole resistance as the first therapeutic choice in all types of invasive Candida infections. Patients with invasive candidiasis and no previous exposure to azoles may receive azoles as initial therapy if they are stable hemodynamically and do not have an increased risk of C. glabrata infection. The group of patients at high risk of
C. glabrata includes patients with cancer or diabetes mellitus, and the elderly [69]. There are trials of newer azoles (posaconazole, ravuconazole, isavuconazole) demonstrating excellent in vitro activity against C. krusei, C. guilliermondii and C. glabrata. They might be alternatives to echinocandins as a first-line therapy [27,191].

Amphotericin B deoxycholate or, preferably, lipid formulations may be considered in infections refractory to other systemic antifungals in Candida endocarditis or Candida endophthalmitis. Intolerance of other classes of antifungals in individuals may also favor the use of amphotericin B lipid formulations. Multidrug-resistant strains with resistance to azoles and echinocandins are encountered with increasing frequency in C. glabrata and C. auris, with amphotericin B lipid formulations successfully used in these cases. Pan-drug-resistant strains of C. auris with no available treatment options have already been reported [192].

The recommended duration of systemic antifungal therapy for candidemia is at least 14 days after the eradication of Candida spp. from the blood and the resolution of all symptoms and signs of infection [69,151]. In deep-seated invasive candidiasis, e.g., chronic hepatosplenic candidiasis or intra-abdominal candidiasis, the duration of treatment normally differs from several weeks to 6–12 months and is individually adjusted. It is guided by the rate of lesion resolution, physicians' personal experience, and scarce and typically non-randomized studies [27].

4. Conclusions

Invasive candidiasis is a major course of morbidity and mortality with an incidence of up to 2.49/1000 admissions and an estimated attributable mortality for candidemia of 10–47% [27,33,34,49]. Five Candida species (C. albicans, C. glabrata, C. parapsilosis, C. krusei, C. tropicalis) are responsible for more than 90% of infections [16,30–32]. The diagnosis of deep-seated organ involvement is challenging, and blood cultures provide positive results in less than 40% of patients without concurrent candidemia [67]. Several non-cultural techniques have been developed in recent years that act as valuable diagnostic tools and are especially useful in excluding the diagnosis of invasive candidiasis due to a high negative predictive value. The combination of two tests—beta-D-glucan and procalcitonin—is highly recommended [27,115]. There is a clear demand for future research and the development of sensitive and precise diagnostic tools. The most promising seem to be omics technologies capable of providing new substances to be applied as valuable diagnostic tests for identification and susceptibility testing in Candida spp., as well as to determine host factors predisposing for infection. There are only four classes of systemic antifungals with echinocandins as the first line, and the use of azoles for de-escalation therapy is most widely adopted [27,180,184,190]. The further search for new classes of antifungals is essential taking into account the potential multi-drug resistance in C. glabrata, demonstrating an increasing frequency of resistance to echinocandins and azoles. Moreover, C. krusei has an intrinsic fluconazole resistance, combined with a reported decreased susceptibility to amphotericin B and flucytosine, and pan-drug resistance is emerging in C. auris [29,193–199].

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References

1. Romo, J.A.; Kumamoto, C.A. On commensalism of Candida. J. Fungi 2020, 6, 16. [CrossRef] [PubMed]

2. Kumamoto, C.A.; Gresnigt, M.S.; Hube, B. The gut, the bad and the harmless: Candida albicans as a commensal and opportunistic pathogen in the intestine. Curr. Opin. Microbiol. 2020, 56, 7–15. [CrossRef]

3. Pérez, J.C. Fungi of the human gut microbiota: Roles and significance. Int. J. Med. Microbiol. 2021, 311, 151490. [CrossRef] [PubMed]

4. Bacali, C.; Vulturaru, R.; Buduru, S.; Cozma, A.; Fodor, A.; Chis, A.; Lucaciu, O.; Damian, L.; Moldovan, M.L. Oral microbiome: Metting to now and befriend neighbours, a biological approach. Biomedicines 2022, 10, 671. [CrossRef] [PubMed]

5. Hameed, S.; Hans, S.; Monasky, R.; Thangamani, S.; Fatima, Z. Understanding human microbiota offers novel and promising therapeutic options against Candida infections. Pathogens 2021, 10, 183. [CrossRef] [PubMed]

6. Boxberger, M.; Cenizo, V.; Cassir, N.; La Scola, B. Challenges in exploring and manipulating the human skin microbiome. Microbiome 2021, 9, 125. [CrossRef]

7. Tortelli, B.A.; Lewis, W.G.; Allsworth, J.E.; Member-Meneh, N.; Foster, L.R.; Reno, H.E.; Peipert, J.F.; Fay, J.C.; Lewis, A.L. Fungal infections in critically ill patients. Intensive Care Med. 2021, 47, 471.e1–471.e9. [CrossRef]

8. Chee, W.J.Y.; Chew, S.Y.; Than, L.T.L. Vaginal microbiota and the potential of Lactobacillus derivatives in maintaining vaginal health. Microb. Cell Fact. 2020, 19, 203. [CrossRef]

9. Kalia, N.; Singh, J.; Kaur, M. Microbiota in vaginal health and pathogenesis of recurrent vulvovaginal infections: A critical review. Ann. Clin. Microbiol. Antimicrob. 2020, 19, 5. [CrossRef]

10. Pellon, A.; Sadeghi Nasab, S.D.; Moyes, D.L. New insights in Candida albicans innate immunity at the mucosa: Toxins, epithelium, metabolism, and beyond. Front. Cell. Infect. Microbiol. 2020, 10, 81. [CrossRef]

11. Lanternier, F.; Cypowyj, S.; Picard, C.; Bustamante, J.; Lortholary, O.; Casanova, J.L.; Puel, A. Primary immunodeficiencies underlying fungal infections. Curr. Opin. Pediatrics 2013, 25, 736–747. [CrossRef] [PubMed]

12. Abd Elaziz, D.; Abd El-Ghany, M.; Meshaal, S.; El Hawary, R.; Lotfy, S.; Galal, N.; Ouf, S.A.; Elmarsafy, A. Fungal infections in primary immunodeficiency diseases. Clin. Immunol. 2020, 219, 108533. [CrossRef] [PubMed]

13. Festekjian, A.; Neely, M. Incidence and predictors of invasive candidiasis associated with candidaemia in children. Mycoses 2011, 54, 146–153. [CrossRef]

14. St-Germain, G.; Laverdière, M.; Pelletier, R.; Bourgault, A.M.; Libman, M.; Lemieux, C.; Noël, G. Prevalence and antifungal susceptibility of 442 Candida isolates from blood and other normally sterile sites: Results of a 2-year (1996 to 1998) multicenter surveillance study in Quebec, Canada. J. Clin. Microbiol. 2001, 39, 949–953. [CrossRef] [PubMed]

15. Pappas, P.G.; Alexander, B.D.; Andes, D.R.; Hadley, S.; Kauffman, C.A.; Freifeld, A.; Anaissie, E.J.; Brumble, L.M.; Herwaldt, L.; Ito, J.; et al. Invasive fungal infections among organ transplant recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin. Infect. Dis. 2010, 50, 1101–1111. [CrossRef]

16. Spampinato, C.; Leonardi, D. Candida infections, causes, targets, and resistance mechanisms: Traditional and alternative antifungal agents. Biomed Res. Int. 2013, 2013, 204237. [CrossRef]

17. Ghanez-Zoubi, N.; Khoury, J.; Arnon, M.; Zorbavel, D.; Geffen, Y.; Paul, M. Risk factors for non-albicans candidemia focusing on prior antifungal and immunosuppressive therapy. Isr. Med. Assoc. J. 2019, 21, 303–307. [PubMed]

18. Yapar, N. Epidemiology and risk factors for invasive candidiasis. Ther. Clin. Risk Manag. 2014, 10, 95–105. [CrossRef]

19. Thomas-Rüddel, D.O.; Schlattmann, P.; Petzet, M.; Kurzai, O.; Bloos, F. Risk factors for invasive Candida infection in critically ill patients: A systematic review and meta-analysis. Chest 2016, 141, 345–355. [CrossRef]

20. Pyrgos, V.; Ratanavanich, K.; Donegan, N.; Veis, J.; Walsh, T.J.; Shoham, S. Candida bloodstream infections in hemodialysis recipients. Med. Mycol. 2009, 47, 463–467. [CrossRef]

21. Girmenia, C.; Finolezzi, E.; Federico, V.; Santopietro, M.; Perrone, S. Invasive Candida infections in patients with haematological malignancies and hematopoietic stem cell transplant recipients: Current epidemiology and therapeutic options. Mediterr. J. Hematol. Infect. Dis. 2011, 3, e2011013. [CrossRef]

22. Lin, Y.-L.; Chen, I.-C.; Yen, J.-H.; Lai, C.-S.; Tsai, Y.-C.; Wu, C.-Y.; Lin, W.-S.; Lin, C.-H.; Huang, Y.-C. Invasive Candidiasis in Hemodialyzed Patients with Major Burns. J. Pers. Med. 2022, 12, 47. [CrossRef] [PubMed]

23. McCarty, T.P.; White, C.M.; Pappas, P.G. Candidemia and Invasive Candidiasis. Infect Dis. Clin. 2021, 35, 389–413. [CrossRef] [PubMed]

24. Zhang, Z.; Zhu, R.; Luan, Z.; Ma, X. Risk of invasive candidiasis with prolonged duration of ICU stay: A systematic review and meta-analysis. BMJ Open 2020, 10, e036452. [CrossRef] [PubMed]

25. Delaloye, J.; Calandra, T. Invasive candidiasis as a cause of sepsis in the critically ill patient. Virulence 2014, 5, 161–169. [CrossRef]

26. Martin-Loeches, I.; Antonelli, M.; Cuenca-Estrella, M.; Dimopoulos, G.; Einay, S.; De Waele, J.J.; Garnacho-Montero, J.; Kanj, S.S.; Machado, F.R.; Montravers, P.; et al. ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. Intensive Care Med. 2019, 45, 789–805. [CrossRef]

27. Pappas, P.; Lionakis, M.; Arendrup, M.; Ostrosky-Zeichner, L.; Kullberg, B.J. Invasive candidiasis. Nat. Rev. Dis. Prim. 2018, 4, 18026. [CrossRef]

28. Turner, S.A.; Butler, G. The Candida pathogenic species complex. Cold Spring Harb. Perspect. Med. 2014, 4, a019778. [CrossRef]
29. Papon, N.; Courдавault, V.; Clastre, M.; Bennett, R.J. Emerging and emerged pathogenic Candida species: Beyond the Candida albicans paradigm. Pls Pathog. 2013, 9, e1003550. [CrossRef]
30. Singh, D.K.; Töth, R.; Gácsér, A. Mechanisms of pathogenic Candida species to evade the host complement attack. Front. Cell. Infect. Microbiol. 2020, 10, 94. [CrossRef]
31. Xiao, Z.; Wang, Q.; Zhu, F.; An, Y. Epidemiology, species distribution, antifungal susceptibility and mortality risk factors of candidemia among critically ill patients in China. Antimicrob. Resist. Infect. Control 2019, 8, 89. [CrossRef] [PubMed]
32. Pappas, P.G. Antifungal clinical trials and guidelines: What we know and do not know. Cold Spring Harb. Perspect. Med. 2014, 4, a019745. [CrossRef] [PubMed]
33. Pfaller, M.A.; Diekema, D.J. Epidemiology of invasive candidiasis: A persistent public health problem. Clin. Microbiol. Rev. 2007, 20, 133–163. [CrossRef] [PubMed]
34. Rossato, L.; Colombo, A.L. Candida auris: What have we learned about its mechanisms of pathogenicity? Front. Microbiol. 2018, 9, 3081. [CrossRef]
35. Du, H.; Bing, J.; Hu, T.; Ennis, C.L.; Nobile, C.J.; Huang, G. Drug resistance and novel therapeutic approaches in invasive candidiasis. Front. Cell. Infect. Microbiol. 2021, 11, 759408. [CrossRef]
36. Keighley, C.; Garnham, K.; Harch, S.A.J.; Robertson, M.; Chaw, K.; Chen, S.C.-A. Candida auris: Diagnostic challenges and emerging opportunities for the clinical microbiology laboratory. Curr. Fungal Infect. Rep. 2021, 15, 116–126. [CrossRef]
37. Lone, S.A.; Ahmad, A. Candida auris—The growing menace to global health. Mycoses 2019, 62, 620–637. [CrossRef]
38. Garcia-Bustos, V.; Cabanero-Navalon, M.D.; Ruiz-Sauri, A.; Ruiz-Gaitán, A.C.; Salavert, M.; Tormo, M.A.; Pemán, J. What do we know about Candida auris? State of the art, knowledge gaps, and future directions. Microorganisms 2021, 9, 2177. [CrossRef]
39. Chatzimoschou, A.; Giampani, A.; Meis, J.F.; Rotilides, E. Activities of nine antifungal agents against Candida auris biofilms. Mycoses 2021, 64, 381–384. [CrossRef]
40. Forsberg, K.; Woodworth, K.; Walters, M.; Berkow, E.L.; Jackson, B.; Chiller, T.; Vallabhaneni, S. Inhibition of Candida auris infection and biofilm formation: Going beyond the surface. Curr. Clin. Microbiol. Rev. 2020, 7, 51–56. [CrossRef]
41. Lara, H.H.; Ixtepan-Turrent, L.; Jose Yacaman, M.; Lopez-Ribot, J. Inhibition of Candida auris biofilm formation on medical and environmental surfaces by silver nanoparticles. ACS Appl. Mater. Interfaces 2020, 12, 21183–21191. [CrossRef] [PubMed]
42. Rodrigues, L.S.; Gazara, R.K.; Passarelli-Araujo, H.; Valengo, A.E.; Pontes, P.V.M.; Nunes-da-Fonseca, R.; de Souza, R.F.; Venâncio, T.M.; Dalla-Costa, L.M. First genome sequences of two multidrug-resistant Candida auris isolates from pediatric patients with candidemia. Front. Microbiol. 2020, 11, 1535. [CrossRef]
43. Belkin, A.; Gazit, Z.; Keller, N.; Ben-Ami, R.; Wieder-Finesod, A.; Novikov, A.; Rahav, G.; Brosh-Nissimov, T. Candida auris infection leading to nosocomial transmission, Israel, 2017. Emerg. Infect. Dis. 2018, 24, 801–804. [CrossRef]
44. Cuervo, G.; García-Vidal, C.; Puig-Asensio, M.; Merino, P.; Vena, A.; Martín-Peña, A.; Montejo, J.M.; Ruiz, A.; Lázaro-Perona, F.; Fortún, J.; et al. Usefulness of guideline recommendations for prognosis in patients with candidiasis. Med. Mycol. 2019, 57, 659–667. [CrossRef]
45. Liu, F.; Zhong, L.; Zhou, F.; Zheng, C.; Zhang, K.; Cai, J.; Zhou, H.; Tang, K.; Dong, Z.; Cui, W.; et al. Clinical features, strain distribution, antifungal resistance and prognosis of patients with non-albicans candidemia: A retrospective observational study. Infect. Drug Resist. 2021, 14, 3233–3246. [CrossRef]
46. Diez, A.; Carrano, G.; Bregón-Villahoz, M.; Cuéllar, M.S.; García-Ruiz, J.C.; Fernandez-de-Larrinoa, I.; Moragues, M.D. Biomarkers for the diagnosis of invasive candidiasis in immunocompetent and immunocompromised patients. Diagn. Microbiol. Infect. Dis. 2021, 101, 115509. [CrossRef]
47. Ahmad, S.; Khan, Z. Invasive candidiasis: A review of nonculture-based laboratory diagnostic methods. Indian J. Med. Microbiol. 2012, 30, 264–269. [CrossRef]
48. Monday, L.M.; Parraga Acosta, T.; Alangaden, G. T2Candida for the diagnosis and management of invasive Candida infections. J. Fungi 2021, 7, 178. [CrossRef] [PubMed]
49. Sakai, D.; Matsumiya, W.; Kusuhara, S.; Nakamura, M. Factors associated with the development of ocular candidiasis and ocular prognosis with echinocandins for therapy. J. Ophthal. Inflamm. Infect. 2021, 11, 17. [CrossRef] [PubMed]
50. Brooks, R.G. Prospective study of Candida endophthalmitis in hospitalized patients with candidiasis. Arch. Intern. Med. 1989, 149, 2226–2228. [CrossRef] [PubMed]
51. Arshad, H.; Garcia, S.; Khaja, M. Case report of invasive, disseminated candidiasis with peripheral nodular cavitary lesions in the lung. Respir. Med. Case Rep. 2016, 20, 34–37. [CrossRef]
52. Chen, C.Y.; Cheng, A.; Tien, F.M.; Lee, P.C.; Tien, H.F.; Sheng, W.H.; Chen, Y.C. Chronic disseminated candidiasis manifesting as hepatosplenic abscesses among patients with hematological malignancies. BMC Infect. Dis. 2019, 19, 635. [CrossRef]
56. Boussen, I.; Lisam, Q.; Raffoux, E.; Di Blasi, R.; Boissel, N.; Oksenhendler, E.; Adès, L.; Xhaard, A.; Bretagne, S.; Alanio, A.; et al. Hepatosplenic candidiasis in patients with hematological malignancies: A 13-year retrospective cohort study. Open Forum Infect. Dis. 2022, 9, 88. [CrossRef]

57. Mikulski, M.; Calandra, T.; Sanguinetti, M.; Poulain, D.; Viscoli, C.; Third European Conference on Infections in Leukemia Group. The use of mannann antigen and anti-mannann antibodies in the diagnosis of invasive candidiasis: Recommendations from the Third European Conference on Infections in Leukemia. Crit. Care 2010, 14, R222. [CrossRef]

58. Xiao, X.F.; Wu, J.X.; Xu, Y.C. Treatment of invasive fungal disease: A case report. World J. Clin. Cases 2019, 7, 2374–2383. [CrossRef]

59. Donnelly, J.P.; Chen, S.C.; Kauffman, C.A.; Steinbach, W.J.; Baddley, J.W.; Verweij, P.E.; Clancy, C.J.; Wingard, J.R.; Lockhart, S.R.; Groll, A.H.; et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin. Infect. Dis. 2020, 71, 1367–1376. [CrossRef]

60. Roberto, A.; Xavier, D.E.; Vidal, E.E.; Vidal, C.; Neves, R.P.; Lima-Neto, R.G. Rapid detection of echinocandins resistance by MALDI-TOF MS in Candida parapsilosis complex. Microorganisms 2020, 8, 109. [CrossRef]

61. De Pauw, B.; Walsh, T.J.; Donnelly, J.P.; Stevens, D.A.; Edwards, J.E.; Calandra, T.; Pappas, P.G.; Maertens, J.; Lortholary, O.; Kauffman, C.A. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin. Infect. Dis. 2008, 46, 1813–1821. [CrossRef] [PubMed]

62. Bassetti, M.; Azoulay, E.; Kullberg, B.J.; Ruhnke, M.; Shoham, S.; Vazquez, J.; Giacobbe, D.R.; Calandra, T.; EORTC/MSGERC Definitions of invasive candidiasis: Summary of activities of the Intensive Care Unit Working Group. Clin. Infect. Dis. 2021, 72, S121–S127. [CrossRef] [PubMed]

63. Adhya, A.K. Grocott methenamine silver positivity in neutrophils. J. Cytol. 2019, 36, 184. [CrossRef] [PubMed]

64. Robinson, J.L.; Davies, H.D.; Barton, M.; O’Brien, K.; Simpson, K.; Asztalos, E.; Synnes, A.; Rubin, E.; Le Saux, N.; Hui, C.; et al. Characteristics and outcome of infants with candiduria in neonatal intensive care—A Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study. BMC Infect. Dis. 2009, 9, 183. [CrossRef] [PubMed]

65. Katsragkou, A.; Fisher, B.T.; Groll, A.H.; Rolides, E.; Walsh, T.J. Diagnostic imaging and invasive fungal diseases in children. J. Pediatr Infect. Dis. Soc. 2017, 6, S22–S31. [CrossRef]

66. Bhattacharya, S.; Sae-Tia, S.; Fries, B.C. Candidiasis and mechanisms of antifungal resistance. Antibiotics 2020, 9, 312. [CrossRef]
81. Pfaffer, M.A.; Diekema, D.J.; Turnidge, J.D.; Castanheira, M.; Jones, R.N. Twenty years of the SENTRY Antifungal Surveillance Program: Results for Candida species from 1997–2016. Open Forum Infect. Dis. 2019, 6, S79–S94. [CrossRef] [PubMed]
82. Montes, K.; Ortiz, B.; Galindo, C.; Figueroa, I.; Braham, S.; Fontecha, G. Identification of Candida species from clinical samples in a Honduran tertiary hospital. Pathogens 2019, 8, 237. [CrossRef] [PubMed]
83. Eraso, E.; Moragues, M.D.; Villar-Vidal, M.; Sahand, I.H.; González-Gómez, N.; Pontón, J.; Quindós, G. Evaluation of the new chromogenic medium Candida ID 2 for isolation and identification of Candida albicans and other medically important Candida species. J. Clin. Microbiol. 2006, 44, 3340–3345. [CrossRef] [PubMed]
84. Ghelardi, E.; Pichieri, G.; Castagna, B.; Barnini, S.; Tavanti, A.; Campa, M. Efficacy of Chromogenic Candida Agar for isolation and presumptive identification of pathogenic yeast species. Clin. Microbiol. Infect. 2008, 14, 141–147. [CrossRef]
85. Ozcan, K.; Ilkit, M.; Ates, A.; Turac-Bicer, A.; Demirhindi, H. Performance of chromogenic Candida agar and CHROMagar Candida in recovery and presumptive identification of monofungal and polyfungal vaginal isolates. Med. Mycol. 2010, 48, 29–34. [CrossRef]
86. Mulet Bayona, J.V.; Salvador García, C.; Torno Palop, N.; Valenti Martín, A.; González Padrón, C.; Coloma Rodríguez, J.; Fernández, J.; Gimeno Cardona, C. Novel chromogenic medium CHROMagarTM Candida Plus for detection of Candida auris and other Candida species from surveillance and environmental samples: A multicenter study. J. Fungi. 2022, 8, 281. [CrossRef] [PubMed]
87. Kim, S.H.; Shin, J.H.; Mok, J.H.; Kim, S.Y.; Song, S.A.; Kim, H.R.; Kook, J.K.; Chang, Y.H.; Bae, I.K.; Lee, K. Misidentification of Candida guilliermondii as C. famata among strains isolated from blood cultures by the VITEK 2 system. BioMed Res. Int. 2014, 2014, 250408. [CrossRef]
88. Huang, Y.S.; Wang, F.D.; Chen, Y.C.; Huang, Y.T.; Hsieh, M.H.; Hii, I.M.; Lee, Y.L.; Ho, M.W.; Liu, C.E.; Chen, Y.H.; et al. High rates of misidentification of uncommon Candida species causing bloodstream infections using conventional phenotypic methods. J. Formos. Med. Assoc. 2021, 120, 1179–1187. [CrossRef]
89. Cheng, J.W.; Yu, S.Y.; Xiao, M.; Wang, H.; Kudinha, T.; Kong, F.; Xu, Y.C. Identification and antifungal susceptibility profile of Candida guilliermondii and presumptive identification of Candida fermentatii from a multicenter study in China. J. Clin. Microbiol. 2016, 54, 2187–2189. [CrossRef]
90. Arastehfar, A.; Daneshnia, F.; Kord, M.; Roudbar, M.; Zarrinfar, H.; Fang, W.; Hashemi, S.J.; Najafzadeh, M.J.; Khodavaisy, S.; Pan, W.; et al. Comparison of 21-Plex PCR and API 20C AUX, MALDI-TOF MS, and rDNA Sequencing for a wide range of clinically isolated yeast species: Improved identification by combining 21-Plex PCR and API 20C AUX as an alternative strategy for developing countries. Front. Cell. Infect. Microbiol. 2019, 9, 21. [CrossRef]
91. Fasciana, T.; Cortegiani, A.; Ippolito, M.; Giarrattano, A.; Di Quattro, O.; Lipari, D.; Graceffa, D.; Giammanco, A. Candida auris: An overview of how to screen, detect, test and control this emerging pathogen. Antibiotics 2020, 9, 778. [CrossRef] [PubMed]
92. Leaw, S.N.; Chang, H.C.; Sun, H.F.; Barton, R.; Bouchara, J.P.; Chang, T.C. Identification of medically important yeast species by sequence analysis of the internal transcribed spacer regions. J. Clin. Microbiol. 2006, 44, 693–699. [CrossRef]
93. Colabella, C.; Casagrande Pierantoni, D.; Corte, L.; Roscini, L.; Conti, A.; Bassetti, M.; Tascini, G.; Robert, C.; Cardinali, G. Single strain high-depth NGS reveals high rDNA (ITS-LSU) variability in the four prevalent pathogenic species of the genus Candida. Microorganisms 2021, 9, 302. [CrossRef] [PubMed]
94. Kwiatkowski, N.P.; Babiker, W.M.; Merz, W.G.; Carroll, K.C.; Zhang, S.X. Evaluation of nucleic acid sequencing of the D1/D2 region of the large subunit of the 28S rDNA and the internal transcribed spacer region using SmartGene IDNS [corrected] software for identification of filamentous fungi in a clinical laboratory. J. Mol. Diagn. 2012, 14, 393–401. [CrossRef]
95. Crossley, B.M.; Bai, J.; Glaser, A.; Maes, R.; Porter, E.; Killian, M.L.; Clement, T.; Toohy-Kirth, K. Guidelines for Sanger sequencing and molecular assay monitoring. J. Vet. Diagn. Investig. 2020, 32, 767–775. [CrossRef]
96. De Cario, R.; Kura, A.; Suraci, S.; Magi, A.; Volta, A.; Marucci, R.; Gori, A.M.; Pepe, G.; Giusti, B.; Sticher, E. Sanger validation of high-throughput sequencing in genetic diagnosis: Still the best practice? Front. Genet. 2020, 11, 592588. [CrossRef]
97. Chen, L.; Cai, Y.; Zhou, G.; Shi, X.; Su, J.; Chen, G.; Lin, K. Rapid Sanger sequencing of the 16S rRNA gene for identification of some common pathogens. PLoS ONE 2014, 9, e88886. [CrossRef]
98. Oviño, M.; Rodríguez-Sánchez, B. MALDI-TOF mass spectrometry in the 21st century clinical microbiology laboratory. Enferm. Infecc. Y Microb. Clin. 2021, 39, 192–200. [CrossRef] [PubMed]
99. Robert, M.G.; Cornet, M.; Hennebique, A.; Rasamoelina, T.; Caspar, Y.; Pondérand, L.; Bidart, M.; Durand, H.; Jacquet, M.; Garnaud, C.; et al. MALDI-TOF MS in a medical mycology laboratory: On stage and backstage. Microorganisms 2021, 9, 1283. [CrossRef]
100. Ceballos-Garzón, A.; Cabrera, E.; Cortes-Fraile, G.C.; León, A.; Aguirre-Guataqui, K.; Linares-Linares, M.Y.; Ariza, B.; Valderrama-Beltrán, S.; Parra-Giraldo, C.M. In-house protocol and performance of MALDI-TOF MS in the early diagnosis of bloodstream infections in a fourth-level hospital in Colombia: Jumping to full use of this technology. Int. J. Infect. Dis. 2020, 101, 85–89. [CrossRef]
101. Yaman, G.; Akyar, I.; Can, S. Evaluation of the MALDI TOF-MS method for identification of Candida strains isolated from blood cultures. Diagn. Microbiol. Infect. Dis. 2012, 73, 65–67. [CrossRef] [PubMed]
102. Camp, I.; Spettel, K.; Willinger, B. Molecular Methods for the diagnosis of invasive candidiasis. J. Fungi 2020, 6, 101. [CrossRef] [PubMed]
103. Wey, S.B.; Mori, M.; Pfaffer, M.A.; Woolson, R.F.; Wenzel, R.P. Risk factors for hospital-acquired candidemia. A matched case-control study. *Arch. Intern. Med.* 1989, 149, 2349–2353. [CrossRef] [PubMed]

104. Brillowska-Dabrowska, A.; Bergmann, O.; Jensen, I.M.; Jarløv, J.O.; Arendrup, M.C. Typing of Candida isolates from patients with invasive infection and concomitant colonization. *Scand. J. Infect. Dis.* 2010, 42, 109–113. [CrossRef]

105. Jensen, R.H.; Johansen, H.K.; Soes, L.M.; Lemming, L.E.; Rosenvinge, F.S.; Nielsen, L.; Olesen, B.; Kristensen, L.; Dzajic, E.; Astvad, K.M.; et al. Posttreatment antifungal resistance among colonizing Candida isolates in candidemia patients: Results from a systematic multicenter study. *Antimicrob. Agents Chemother.* 2015, 60, 1500–1508. [CrossRef] [PubMed]

106. Dupuis, C.; Le Bihan, C.; Maubon, D.; Calvet, L.; Ruckly, S.; Schwebel, C.; Bouadma, L.; Azoulay, E.; Cornet, M.; Timsit, J.F.; et al. Performance of repeated measures of (1-3)-β-D-Glucan, mannan antigen, and antimannan antibodies for the diagnosis of invasive candidiasis in ICU patients: A preplanned ancillary analysis of the EMPIRICUS randomized clinical trial. *Open Forum Infect. Dis.* 2021, 8, ofab080. [CrossRef] [PubMed]

107. Li, F.; Yu, X.; Ye, L.; Zhou, G.; Wang, L.; Luo, Y. Clinical value of (1,3)-β-D-glucan, mannan, antimannan IgG and IgM antibodies in diagnosis of invasive candidiasis. *Med. Mycol.* 2019, 57, 976–986. [CrossRef]

108. León, C.; Ruiz-Santana, S.; Saavedra, P.; Castro, C.; Loza, A.; Zakariya, I.; Ubeda, A.; Parra, M.; Macías, D.; Tomás, J.I.; et al. Contribution of Candida biomarkers and DNA detection to the diagnosis of invasive candidiasis in ICU patients with severe abdominal conditions. *Crit. Care* 2016, 20, 149. [CrossRef]

109. Meng, Y.; Kang, M.; Li, D.; Wang, T.; Kuang, Z.; Ma, Y. Performance of a new Candida anti-mannan IgM and IgG assays in the diagnosis of candidemia. *Rev. Inst. Med. Trop. Sao Paulo* 2020, 62, e25. [CrossRef]

110. Hanson, K.E.; Pfeiffer, C.D.; Lease, E.D.; Balch, A.H.; Zaas, A.K.; Perfect, J.R.; Alexander, B.D. β-D-glucan surveillance with preemptive anidulafungin for invasive candidiasis in intensive care unit patients: A randomized pilot study. *PLoS ONE* 2012, 7, e42282. [CrossRef] [PubMed]

111. Tissot, F.; Lamothe, F.; Hauser, P.M.; Orasch, C.; Flücker, U.; Siegemund, M.; Zimmerli, S.; Calandra, T.; Bille, J.; Eggimann, P.; et al. β-glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. *Am. J. Respir. Crit. Care Med.* 2013, 188, 1100–1109. [CrossRef]

112. Hartl, B.; Zeller, I.; Manhart, A.; Selitsch, B.; Lass-Flörl, C.; Willinger, B. A Retrospective assessment of four antigen assays for the detection of invasive candidiasis among high-risk hospitalized patients. *Mycopathologia* 2018, 183, 513–519. [CrossRef] [PubMed]

113. Mohr, J.F.; Sims, C.; Paetznick, V.; Rodríguez, J.; Finkelman, M.A.; Rex, J.H.; Ostrosky-Zeichner, L. Prospective survey of (1→3)-beta-D-glucan and its relationship to invasive candidiasis in the surgical intensive care unit setting. *J. Clin. Microbiol.* 2011, 49, 58–61. [CrossRef] [PubMed]

114. Martínez-Jiménez, M.C.; Muñoz, P.; Valerio, M.; Vena, A.; Guinea, J.; Bouza, E. Combination of Candida biomarkers in patients receiving empirical antifungal therapy in a Spanish tertiary hospital: A potential role in reducing the duration of treatment. *J. Antimicrob. Chemother.* 2015, 70, 3107–3115. [CrossRef]

115. Giacobbe, D.R.; Mikulska, M.; Tumbarello, M.; Spadaro, M.; Losito, A.R.; Macis, A.; Marchese, A.; Bruzzone, M.; et al. Combined use of serum (1,3)-β-D-glucan and procalcitonin for the early differential diagnosis between candidemia and bacteraemia in intensive care units. *Crit. Care* 2017, 21, 176. [CrossRef]

116. Fortún, J.; Meije, Y.; Buitrago, M.J.; Gago, S.; Bernal-Martínez, L.; Pemán, J.; Pérez, M.; Gómez-G Pedrosa, E.; Madrid, N.; Pintado, V.; et al. Clinical validation of a multiplex real-time PCR assay for detection of invasive candidiasis in intensive care unit patients. *J. Antimicrob. Chemother.* 2014, 69, 3314–3314. [CrossRef]

117. Parra-Sánchez, M.; Zakariya-Yousef Brelal, I.; Castro Méndez, C.; García-Rey, S.; Loza Vazquez, A.; Ubeda Iglesias, A.; Macias Guerrero, D.; Romero Mejías, A.; León Gil, C.; Martin-Mazuelos, E.; et al. *Candida albicans* germ-tube antibody: Evaluation of a new automatic assay for diagnosing invasive candidiasis in ICU patients. *Mycopathologia* 2017, 182, 645–652. [CrossRef] [PubMed]

118. Pfeiffer, C.D.; Samsa, G.P.; Schell, W.A.; Reller, L.B.; Perfect, J.R.; Alexander, B.D. Quantitation of Candida CFU in initial positive Sautour, M.; Lemaître, J.-P.; Ranjard, L.; Truntzer, C.; Basmaciyan, L.; Depret, G.; Kristensen, L.; Dzajic, E.; Astvad, K.M.; et al. Posttreatment antifungal resistance among colonizing Candida isolates in candidemia patients: Results from a systematic multicenter study. *Antimicrob. Agents Chemother.* 2015, 60, 1500–1508. [CrossRef] [PubMed]

119. Dupuis, C.; Le Bihan, C.; Maubon, D.; Calvet, L.; Ruckly, S.; Schwebel, C.; Bouadma, L.; Azoulay, E.; Cornet, M.; Timsit, J.F.; et al. Performance of repeated measures of (1-3)-β-D-Glucan, mannan antigen, and antimannan antibodies for the diagnosis of invasive candidiasis in ICU patients: A preplanned ancillary analysis of the EMPIRICUS randomized clinical trial. *Open Forum Infect. Dis.* 2021, 8, ofab080. [CrossRef] [PubMed]

120. Chang, S.S.; Hsieh, W.H.; Liu, T.S.; Lee, S.H.; Wang, C.H.; Chou, H.C.; Yeo, Y.H.; Tseng, C.P.; Lee, C.C. Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis—A systematic review and meta-analysis. *PLoS ONE* 2013, 8, e62323. [CrossRef]

121. Jordana-Lluch, E.; Gímenez, E.; Quesada, M.D.; Rivaya, B.; Armengol, A.; Ausina, V. Evaluation of the broad-range PCR/ESI-MS technology in blood specimens for the molecular diagnosis of bloodstream infections. *PLoS ONE* 2015, 10, e0140865. [CrossRef] [PubMed]

122. Desmet, S.; Maertens, J.; Bueselinck, K.; Lagrou, K. Broad-Range PCR Coupled with electrospray ionization time of flight mass spectrometry for detection of bacteremia and fungemia in patients with neutropenic fever. *J. Clin. Microbiol.* 2016, 54, 2513–2520. [CrossRef] [PubMed]

123. Metzgar, D.; Frinder, M.W.; Rothman, R.E.; Peterson, S.; Carroll, K.C.; Zhang, S.X.; Avornu, G.D.; Rounds, M.A.; Carolan, H.E.; Toleño, D.M.; et al. The IRIDICA BAC BS1 assay: Rapid, sensitive and culture-independent identification of bacteria and candida in blood. *PLoS ONE* 2016, 11, e0158186. [CrossRef] [PubMed]

124. White, P.L.; Hibbitts, S.J.; Perry, M.D.; Green, J.; Stirling, E.; Woodford, L.; McNay, G.; Stevenson, R.; Barnes, R.A. Evaluation of a commercially developed semiautomated PCR-surface-enhanced raman scattering assay for diagnosis of invasive fungal disease. *J. Clin. Microbiol.* 2014, 52, 3536–3543. [CrossRef] [PubMed]
125. Mylonakis, E.; Clancy, C.J.; Ostrosky-Zeichner, L.; Garey, K.W.; Alangaden, G.J.; Vazquez, J.A.; Groeger, J.S.; Judson, M.A.; Vinagre, Y.M.; Heard, S.O.; et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: A clinical trial. Clin. Infect. Dis. 2015, 60, 892–899. [CrossRef] [PubMed]

126. Kriforis, A.; Ulberg, M.; Castegren, M.; Petersson, J.; Sparrelid, E.; Hammarström, H.; Sjölin, J.; Özençi, V.; Bliennow, O. T2 Candida assay in the diagnosis of intraabdominal candidiasis: A prospective multicenter study. J. Fungi 2022, 8, 86. [CrossRef]

127. Herman, A.; Herman, A. P. Could Candida Overgrowth Be Involved in the Pathophysiology of Autism? J. Clin. Med. 2022, 11, 442. [CrossRef]

128. Li, L.; Liao, Z.; Yang, Y.; Lv, L.; Cao, Y.; Zhu, Z. Metabolomic profiling for the identification of potential biomarkers involved in a laboratory azole resistance in Candida albicans. PLoS ONE 2018, 13, e0192328. [CrossRef]

129. Liu, R.; Bao, Z.X.; Zhao, P.J.; Li, G.H. Advances in the study of metabolomics and metabolites in some species interactions. Molecules 2021, 26, 3311. [CrossRef]

130. Smeekens, S.P.; van de Veerdonk, F.L.; Netea, M.G. An omics perspective on Candida infections: Toward next-generation diagnosis and therapy. Front. Microbiol. 2016, 7, 154. [CrossRef]

131. Kumar, V.; Cheng, S.C.; Johnson, M.D.; Smeekens, S.P.; Wojtowicz, A.; Giamarellos-Bourboulis, E.; Karjalainen, J.; Franke, L.; Witthoff, S.; Plantinga, T.S.; et al. Immunochip SNP array identifies novel genetic variants conferring susceptibility to candidaemia. Nat. Commun. 2014, 5, 4675. [CrossRef] [PubMed]

132. CLSI Performance Standards for Antifungal Susceptibility Testing of Yeasts, 2nd ed.; CLSI supplement M60; Clinical and Laboratory Standards Institute (CLSI): Wayne, PA, USA, 2020.

133. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint Tables for Interpretation of MICs for Antifungal Agents, Version 10.0. 2020. Available online: http://www.eucast.org/astoffungi/clinicalbreakpointsforantifungals/ (accessed on 14 April 2022).

134. Berkow, E.L.; Lockhart, S.R.; Ostrosky-Zeichner, L. Antifungal susceptibility testing: Current approaches. Clin. Microbiol. Rev. 2020, 33, e00069-19. [CrossRef] [PubMed]

135. Nunnally, N.S.; Dampt, T.; Lockhart, S.R.; Berkow, E.L. Categorizing susceptibility of clinical isolates of Candida auris to amphotericin B, caspofungin, and fluconazole by use of the CLSI M44-A2 disk diffusion method. J. Clin. Microbiol. 2021, 59, e02355-20. [CrossRef] [PubMed]

136. CDC. Antifungal Susceptibility Testing and Interpretation. Available online: https://www.cdc.gov/fungal/candida-aursis-c-aursis-antifungal.html (accessed on 14 April 2022).

137. Aigner, M.; Erbeznik, T.; Gschwentner, M.; Lass-Flörl, C. Etest and Sensititre YeastOne susceptibility testing of echinocandins against Candida species from a single center in Austria. Antimicrob. Agents Chemother. 2017, 61, e00512-17. [CrossRef]

138. Altinbaş, R.; Barış, A.; Şen, S.; Öztürk, R.; Kiraz, N. Comparison of the Sensititre YeastOne antifungal method with the CLSI M27-A3 reference method to determine the activity of antifungal agents against clinical isolates of Candida spp. Turk. J. Med. Sci. 2020, 50, 2024–2031. [CrossRef]

139. Córdoba, S.; Abiega, C.; Agorio, I.; Amigot, S.; Ardizzoni, K.; Giusiano, G.; Guelfand, L.; López Moral, L.; Maldonado, I.; Pineda, G.; et al. Utilidad del panel Sensititre YeastOne® para detectar especies de Candida resistentes a los antifúngicos [Usefulness of the Sensititre YeastOne®panel to detect Candida species resistant to antifungal drugs]. Rev. Argent. Microbiol. 2022, 54, 9–14. [CrossRef]

140. Siqueira, R.A.; Doi, A.M.; de Petrus Crossara, P.P.; Koga, P.C.M.; Marques, A.G.; Nunes, F.G.; Pasternak, J.; Martinod, M.D.V. Evaluation of two commercial methods for the susceptibility testing of Candida species: Vitek 2® and Sensititre YeastOne®. Rev. Iberoam. Micr. 2018, 35, 83–87. [CrossRef] [PubMed]

141. Arendrup, M.C.; Prakash, A.; Meletiadis, J.; Sharma, C.; Chowdhary, A. Comparison of EUCAST and CLSI reference microdilution MICs of eight antifungal compounds for Candida auris and associated tentative epidemiological cutoff values. Antimicrob. Agents Chemother. 2017, 61, e00485-17. [CrossRef] [PubMed]

142. Magobo, R.E.; Corcoran, C.; Seetharam, S.; Govender, N.P. Candida auris-associated candidemia, South Africa. Emerg. Infect. Dis. 2014, 20, 1250–1251. [CrossRef]

143. Kathuria, S.; Singh, P.K.; Sharma, C.; Prakash, A.; Masih, A.; Kumar, A.; Meis, J.F.; Chowdhary, A. Multidrug-resistant Candida auris misidentified as Candida haemulonii: Characterization by Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry and DNA sequencing and its antifungal susceptibility profile variability by Vitek 2, CLSI broth microdilution, and Etest method. J. Clin. Microbiol. 2015, 53, 1823–1830. [CrossRef]

144. Kritikos, A.; Neofytos, D.; Khanna, N.; Schreiber, P.W.; Boggian, K.; Bille, J.; Schrenzel, J.; Mühlethaler, K.; Zbinden, R.; Bruderer, T.; et al. Accuracy of Sensititre YeastOne echinocandins epidemiological cut-off values for identification of FKS mutant Candida albicans and Candida glabrata: A ten year national survey of the Fungal Infection Network of Switzerland (FUNGINOS). Clin. Microbiol. Infect. 2018, 24, 1214. [CrossRef] [PubMed]

145. Dalyan Cilo, B.; Ener, B. Comparison of Clinical Laboratory Standards Institute (CLSI) Microdilution method and VITEK 2 automated antifungal susceptibility system for the determination of antifungal susceptibility of Candida species. Cureus 2021, 13, e20220. [CrossRef] [PubMed]

146. Calandra, T.; Roberts, J.A.; Antonelli, M.; Bassetti, M.; Vincent, J.L. Diagnosis and management of invasive candidiasis in the ICU: An updated approach to an old enemy. Crit. Care 2016, 20, 125. [CrossRef] [PubMed]
147. Jung, P.; Mischo, C.E.; Gunaratnam, G.; Spengler, C.; Becker, S.L.; Hube, B.; Jacobs, K.; Bischoff, M. Candida albicans adhesion to central venous catheters: Impact of blood plasma-driven germ tube formation and pathogen-derived adhesins. Virulence 2020, 11, 1453–1465. [CrossRef]

148. Kollef, M.; Micek, S.; Hampton, N.; Doherty, J.A.; Kumar, A. Septic shock attributed to Candida infection: Importance of empiric therapy and source control. Clin. Infect. Dis. 2012, 54, 1739–1746. [CrossRef] [PubMed]

149. Anderson, T.M.; Clay, M.C.; Cioffi, A.G.; Diaz, K.A.; Hisao, G.S.; Tuttle, M.D.; Nieuwkoop, A.J.; Comellas, G.; Maryum, N.; Vergidis, P.; Clancy, C.J.; Shields, R.K.; Park, S.Y.; Wildfeuer, B.N.; Simmons, R.L.; Nguyen, M.H. Intra-abdominal candidiasis: The importance of early source control and antifungal treatment. PLoS ONE 2016, 11, e0153247. [CrossRef]

150. Andes, D.R.; Safdar, N.; Baddley, J.; Playford, G.; Reboi, A.C.; Rex, J.H.; Sobel, J.D.; Pappas, P.G.; Kullberg, B.J.; Mycoses Study Group. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: A patient-level quantitative review of randomized trials. Clin. Infect. Dis. 2012, 54, 1110–1122. [CrossRef]

151. Cornely, O.A.; Bassetti, M.; Calandra, T.; Garbino, J.; Kullberg, B.J.; Lortholary, O.; Meersseman, W.; Akova, M.; Arendrup, M.C.; Arikan-Akdagli, S.; et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: Non-neutropenic adult patients. Clin. Microbiol. Infect. 2012, 18, 19–37. [CrossRef] [PubMed]

152. Cavassin, F.B.; Baudi-Carneiro, J.L.; Vilas-Boas, R.R.; Queiroz-Telles, F. Sixty years of amphotericin B: An overview of the main antifungal agent used to treat invasive fungal infections. Infect. Dis. Ther. 2021, 10, 115–147. [CrossRef]

153. Anderson, T.M.; Clay, M.C.; Cioffi, A.G.; Diaz, K.A.; Hisao, G.S.; Tuttle, M.D.; Nieuwkoop, A.J.; Comellas, G.; Maryum, N.; Wang, S.; et al. Amphotericin forms an extramembranous and fungicidal sterol sponge. Nat. Chem. Biol. 2014, 10, 400–406. [CrossRef]

154. Robbins, N.; Caplan, T.; Cowen, L.E. Molecular evolution of antifungal drug resistance. Annu. Rev. Microbiol. 2017, 71, 753–775. [CrossRef] [PubMed]

155. Apsemidou, A.; Füller, M.A.; Idelevich, E.A.; Kurzai, O.; Tragiannidis, A.; Groll, A.H. Non-albicans Candida species: A current perspective. Front. Microbiol. 2017, 8, 380. [CrossRef] [PubMed]

156. Caputo, R.; Asprea, M.; Giovannetti, L.; Messori, A. Nephrotoxicity of three formulations of amphotericin B: Trial sequential analysis. Arch. Med. Sci. 2020, 16, 1493–1496. [CrossRef]

157. Abdel-Hafez, Y.; Sijaj, H.; Janajri, M.; Abu-Baker, Y.; Nazzal, Z.; Hamdan, Z.; Adwan, R.; Aiesh, B.M.; Anaya, A.I. Tolerability and epidemiology of nephrotoxicity associated with conventional amphotericin B therapy: A retrospective study in tertiary care centers in Palestine. BMC Nephrol. 2022, 23, 132. [CrossRef]

158. Peyclit, L.; Yousfi, H.; Rolain, J.-M.; Bittar, F. Drug repurposing in medical mycology: Identification of compounds as potential antifungals to overcome the emergence of multidrug-resistant fungi. Pharmaceuticals 2020, 12, 29. [CrossRef] [PubMed]

159. Galia, L.; Pezzani, M.D.; Compri, M.; Callegari, A.; Rajendran, N.B.; Carrara, E.; Tacconelli, E.; The COMBACTE MAGNET EPI-Net Network. Surveillance of Antifungal Resistance in Candidemia Fails to Inform Antifungal Stewardship in European Countries. J. Fungi 2020, 6, 909. [CrossRef] [PubMed]

160. Testoni, D.; Smith, P.B.; Benjamin, D.K., Jr. The use of antifungal therapy in neonatal intensive care. Expert Opin. Pharmacother. 2015, 16, 1035–1048. [CrossRef]

161. Vertes, A.; van Der Sijs, H.; Guchelaar, H.J. Flucytosine: Correlation between toxicity and pharmacokinetic parameters. Chemotherapy 2000, 46, 86–94. [CrossRef]

162. Vitale, R.G. Role of antifungal combinations in difficult to treat Candida infections. J. Fungi 2021, 7, 731. [CrossRef] [PubMed]

163. Hassanmoghadam, F.; Shokohi, T.; Hedayati, M.T.; Aslani, N.; Haghani, I.; Nabili, M.; Lotfali, E.; Davari, A.; Moazeni, M. High prevalence of itraconazole resistance among Candida parapsilosis isolated from Iran. Antimicrob. Agents Chemother. 2021, 65, e01992-20. [CrossRef]

164. Miesel, L.; Cushion, M.T.; Ashbaugh, A.; Lopez, S.R.; Ong, V. Efficacy of rezafungin in prophylactic mouse models of invasive Candidiasis, Aspergillosis, and Pneumocystis pneumonia. Antimicrob. Agents Chemother. 2021, 65, e01992-20. [CrossRef]
173. Lepak, A.J.; Zhao, M.; Andes, D.R. Determination of pharmacodynamic target exposures for rezafungin against Candida tropicalis and Candida dubliniensis in the neutropenic mouse disseminated candidiasis model. *Antimicrob. Agents Chemother.* 2019, 63, e01536-19. [CrossRef]

174. Pfaller, M.A.; Carvalhaes, C.; Messer, S.A.; Rhomberg, P.R.; Castanheira, M. Activity of a long-acting echinocandin, rezafungin, and comparator antifungal agents tested against contemporary unvasive fungal isolates (SENTRY program, 2016 to 2018). *Antimicrob. Agents Chemother.* 2020, 64, e00099-20. [CrossRef]

175. Farhadi, Z.; Farhadi, T.; Hashemian, S.M. Virtual screening for potential inhibitors of β(1,3)-D-glucan synthase as drug candidates against fungal cell wall. *J. Drug Assess.* 2020, 9, 52–59. [CrossRef] [PubMed]

176. Szymański, M.; Chmielewska, S.; Czyżewska, U.; Malinowska, M.; Tylicki, A. Echinocandins—Structure, mechanism of action and use in antifungal therapy. *J. Enzym. Inhib. Med. Chem.* 2022, 37, 876–894. [CrossRef] [PubMed]

177. Hautala, N.; Köykkä, H.; Siiskonen, M.; Saari, J.; Kauranen, J.; Hautala, T. Effect of first-line antifungal treatment onocular complication risk in *Candida* or yeast blood stream infection. *BMJ Open Ophthalmol.* 2021, 6, e000837. [CrossRef] [PubMed]

178. Taur, Y.; Cohen, N.; Dubnow, S.; Paskovaty, A.; Seo, S.K. Effect of antifungal therapy timing on mortality in cancer patients with candidemia. *Antimicrob Agents Chemother.* 2010, 54, 184–190. [CrossRef] [PubMed]

179. Mroczyńska, M.; Brillovska-Dąbrowska, A. Review on current status of echinocandins use. *Antibiotic* 2020, 9, 227. [CrossRef]

180. Bretagne, S.; Desnos-Ollivier, M.; Sitbon, K.; Lortholary, O.; Che, D.; Dromer, F.; Participants of the YEASTS. No impact of antifungal agents against contemporary unvasive fungal isolates (SENTRY program, 2016 to 2018). *Antimicrob. Agents Chemother.* 2020, 64, e00099-20. [CrossRef]

181. Kontoyiannis, D.P.; Bassetti, M.; Nucci, M.; Capparella, M.R.; Yan, J.L.; Aram, J.; Hogan, P.A. Anidulafungin for the treatment of *Candida* parapsilosis bloodstream infection: A propensity score analysis. *Clin. Infect. Dis.* 2020, 93, 15–21. [CrossRef]

182. Reboli, A.C.; Shorr, A.F.; Rotstein, C.; Pappas, P.G.; Kett, D.H.; Schlamm, H.T.; Reisman, A.L.; Biswas, P.; Walsh, T.J. Anidulafungin compared with fluconazole for treatment of candidemia and other forms of invasive candidiasis caused by *Candida albicans*: A multivariate analysis of factors associated with improved outcome. *BMJ Infect. Dis.* 2011, 11, 261. [CrossRef]

183. Kullberg, B.J.; Sobel, J.D.; Ruhnke, M.; Pappas, P.G.; Viscoli, C.; Rex, J.H.; Cleary, J.D.; Rubinstein, E.; Church, L.W.; Brown, J.M.; et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidemia in non-neutropenic patients: A randomised non-inferiority trial. *Lancet* 2005, 366, 1435–1442. [CrossRef]

184. Vazquez, J.; Reboli, A.C.; Pappas, P.G.; Patterson, T.F.; Reinhardt, J.; Chin-Hong, P.; Tobin, E.; Kett, D.H.; Biswas, P.; Swanson, R. Evaluation of an early step-down strategy from intravenous anidulafungin to oral therapy for the treatment of candidemia and other forms of invasive candidiasis: Results from an open-label trial. *BMJ Infect. Dis.* 2014, 14, 97. [CrossRef] [PubMed]

185. Pappas, P.G.; Rotstein, C.M.; Betts, R.F.; Nucci, M.; Talwar, D.; De Waele, J.J.; Vazquez, J.A.; Dupont, B.F.; Horn, D.L.; Ostrosky-Zeichner, L.; et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin. Infect. Dis.* 2007, 45, 883–893. [CrossRef] [PubMed]

186. Kullberg, B.J.; Viscoli, C.; Pappas, P.G.; Vazquez, J.; Ostrosky-Zeichner, L.; Rotstein, C.; Sobel, J.D.; Herbrecht, R.; Rahav, G.; Jaruratanasirikul, S.; et al. Isavuconazole versus caspofungin in the treatment of candidemia and other forms of invasive candidiasis: The ACTIVE trial. *Clin. Infect. Dis.* 1998–1999. [CrossRef] [PubMed]

187. Fernández-Ruiz, M.; Aguado, J.M.; Almirante, B.; Lora-Pablos, D.; Padilla, B.; Puig-Asensio, M.; Montejo, M.; García-Rodríguez, J.; Pemán, J.; Ruiz Pérez de Pipaón, M.; et al. Initial use of echinocandins does not negatively influence outcome in Candida parapsilosis bloodstream infection: A propensity score analysis. *Clin. Infect. Dis.* 2014, 58, 1413–1421. [CrossRef]

188. Kontoyiannis, D.P.; Bassetti, M.; Nucci, M.; Capparella, M.R.; Yan, J.L.; Aram, J.; Hogan, P.A. Anidulafungin for the treatment of candidaemia caused by *Candida parapsilosis*: Analysis of pooled data from six prospective clinical studies. *Mycoses* 2017, 60, 663–667. [CrossRef]

189. Chiotos, K.; Vendetti, N.; Zaoutis, T.E.; Baddley, J.; Ostrosky-Zeichner, L.; Pappas, P.; Fisher, B.T. Comparative effectiveness of echinocandins versus fluconazole therapy for the treatment of adult candidemia due to Candida parapsilosis: A retrospective observational cohort study of the Mycoses Study Group (MSG-12). *J. Antimicrob. Chemother.* 2016, 71, 3536–3539. [CrossRef]

190. Kullberg, B.J.; Vazquez, J.; Mootsikapun, P.; Nucci, M.; Paiva, J.A.; Garbino, J.; Yan, J.L.; Aram, J.; Capparella, M.R.; Conte, U.; et al. Efficacy of anidulafungin in 539 patients with invasive candidiasis: A patient-level pooled analysis of six clinical trials. *J. Antimicrob. Chemother.* 2017, 72, 2368–2377. [CrossRef] [PubMed]

191. Pfaller, M.A.; Diekema, D.J.; Gibbs, D.L.; Newell, V.A.; Nagy, E.; Dobiasova, S.; Rinaldi, M.; Barton, R.; Veselov, A.; Global Antifungal Surveillance Group. Candida krusei, a multidrug-resistant opportunistic fungal pathogen: Geographic and temporal trends from the ARTEMIS DISK Antifungal Surveillance Program, 2001 to 2005. *J. Clin. Microbiol.* 2008, 46, 515–521. [CrossRef]

192. Ademe, M.; Girma, F. *Candida auris*: From multidrug resistance to pan-resistant strains. *Infect. Drug Resist.* 2020, 13, 1287–1294. [CrossRef]

193. McCarthy, T.P.; Pappas, P.G. Antifungal Pipeline. *Front. Cell. Infect. Microbiol.* 2021, 11, 732223. [CrossRef] [PubMed]

194. Wang, Q.; Li, Y.; Cai, X.; Li, R.; Zheng, B.; Yang, E.; Liang, T.; Yang, X.; Wan, Z.; Liu, W. Two sequential clinical isolates of *Candida glabrata* with multidrug-resistance to posaconazole and echinocandins. *Antibiotics* 2021, 10, 1217. [CrossRef]

195. Bandara, N.; Samaranayake, L. Emerging and future strategies in the management of recalcitrant *Candida auris*. *Med. Mycol.* 2022, 60, myac008. [CrossRef] [PubMed]
196. Centre for Disease Prevention and Control. *Candida auris* Outbreak in Healthcare in Northern Italy, 2019–2021; ECDC: Stockholm, Sweden, 2022.

197. Černáková, L.; Roudbary, M.; Brás, S.; Tafaj, S.; Rodrigues, C.F. *Candida auris*: A quick review on identification, current treatments, and challenges. *Int. J. Mol. Sci.* 2021, 22, 4470. [CrossRef] [PubMed]

198. Denning, D.W. Antifungal drug resistance: An update. *Eur. J. Hosp. Pharm.* 2022, 29, 109–112. [CrossRef] [PubMed]

199. Jamiu, A.T.; Albertyn, J.; Sebolai, O.M.; Pohl, C.H. Update on *Candida krusei*, a potential multidrug-resistant pathogen. *Med. Mycol.* 2021, 59, 14–30. [CrossRef]