APPLICATION TO ADD ECHINOCANDINS TO THE ESSENTIAL LIST OF MEDICINES FOR TREATMENT OF FUNGAL DISEASES

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2 Summary statement of the proposal for inclusion, change or deletion.

The echinocandins are most effective for *Candida* and *Aspergillus* infections. Candidemia is one of the most common hospital-associated bloodstream infections being the fourth to the seventh cause of septicaemia worldwide for more than one and a half decades (1). Notably, *Candida* spp. is a major pathogen in neonatology and paediatrics population. The estimated candidaemia annual incidence is from 374,000 to 897,410 cases per year with a mortality range of 46-75% (2–5). Given a blood culture sensitivity for invasive candidiasis including intra-abdominal candidiasis complicating major abdominal surgery of ~40% (6–8), the incidence is probably 934,800 to 2,243,500 cases per year. *Aspergillus* spp. are the most common filamentous fungi pathogen affecting multiple patient groups including leukaemia and lymphoma, transplant recipients, lung cancer, advanced HIV disease, chronic obstructive pulmonary disease and Covid-19 and influenza severely ill patients. In leukaemia, lung cancer HIV and COPD the minimal annual incidence is 860,000 and with other risk groups not accounted for, the total is >1 million and is almost always fatal unless treated (9,10). Chronic pulmonary aspergillosis in non-immunocompromised people is estimated to have a global prevalence of 2 to 4 million, and an annual 15% mortality (11).

The latest clinical practice guidelines for the management of *Candida* spp. and *Aspergillus* spp. infections recommend echinocandins as first treatment option for invasive candidiasis, for empiric therapy for suspected candidiasis and for salvage treatment of invasive aspergillosis refractory to azole drugs. Since these recommendations, echinocandins have displaced other antifungals as treatment options, since they are fungicidal against the majority of *Candida* spp., but less toxic than amphotericin B. Moreover, they have many fewer drug interactions than the azole drugs. In addition, they have a low resistance rate that differentiates echinocandins from azoles that have alarming resistance rates world-wide.

This application is intended to include echinocandins in the list of WHO list of essential medicines for adults (WHO EML) and children (WHO EMLc) considering that this class of antifungals has several advantages over the azoles and polyenes including:

- Echinocandin drugs are fungicidal against most *Candida* spp. (not fungistatic as azole drugs)(12).
- They are efficacious against almost all *Candida* spp., including intrinsic and secondary azole resistant strains, such as most strains of *Candida auris* (13–15).
- These drugs also show *in vitro* activity against some filamentous fungi including *Aspergillus* spp. (16) and are recommended by different practice guidelines as salvage therapy (either alone or in combination with other drugs) against invasive aspergillosis and chronic pulmonary aspergillosis (17–19).
- These drugs are recommended to treat candidemia in neutropenic and non-neutropenic patients, adults and children (caspofungin and micafungin), including neonates (micafungin) (20).
- Echinocandins have low rates of adverse effects (21–27) since they act by inhibiting the production of the main component of the Ascomycetes fungal cell wall, β 1,3-glucans. This molecule is absent in mammalian cells (28–30).
- Resistance prevalence to this class of antifungals is low and echinocandin resistant mutants show reduced fitness when compared with susceptible strains (28,30–38).
- Echinocandins are not substrates of fungal efflux pumps, making them active against fungal strains harbouring overexpression of these pumps as a key mechanism of azole antifungal resistance (39,40).

The Global Action Fund for Fungal Infections (GAFFI) recommends that the echinocandin class is considered essential therapy for:

- Invasive candidiasis in adults and children
- Invasive candidiasis and candidaemia in neonates (micafungin only)
- Oesophageal candidiasis in patients unresponsive to azoles
- Invasive and chronic pulmonary aspergillosis in patients refractory to azole therapy, intolerant to azoles and in those with azole resistant infections

- As prophylaxis in neutropenic patients in whom azoles are contra-indicated.

3 Relevant WHO technical department and focal point (if applicable).

- Not applicable

4 Name of organization(s) consulted and/or supporting the application.

Global Action Fund for Fungal Infection (GAFFI), Rue Le Corbusier 12, 1208 Geneva, Switzerland in association with the Mycology and Molecular Diagnostics Laboratory, Facultad de Bioquímica y Ciencias Biológicas de la Universidad Nacional del Litoral - Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Ciudad Universitaria UNL, Santa Fe (CP3000) Argentina.

- Guillermo Garcia Effron (ggarcia@unl.edu.ar)
- David W. Denning (ddenning@gaffi.org)
- Juan Luis Rodriguez Tudela (jlrodrigueztudela@gaffi.org)

5 International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

- **Anidulafungin**
  - **ATC Code**: J02AX06
  - **INN Code**: 7795 (proposed list 81/recommended list 43)

- **Caspofungin**
  - **ATC Code:** J02AX04.
  - **INN Code:** 7778 (proposed list 80/recommended list 42).

- **Micafungin**
  - **ATC Code**: J02AX05
  - **INN Code**: 8069 (proposed list 84/recommended list 46)

6 Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Echinocandins dosing presentations are not different if they are intended to be used in adults or in children. For anidulafungin there is only one presentation and for caspofungin and micafungin there are two. The reason of these differences is that for anidulafungin and caspofungin a loading dose (200 mg/day and 70 mg/day, respectively) are recommended. Thus, caspofungin second presentation (70 mg) is on the market as a loading dose vial while for anidulafungin is not necessary since 2 complete 100 mg vials are used as loading dose. Moreover, after the loading dose, caspofungin dose should be adjusted to 70mg/day in patients weighting 80Kg or more.

On the other hand, micafungin does not need a loading dose to start the treatment. However, doses of 50 mg/day, 100 mg/day and 150 mg/day were recommended depending on the fungal infection.

More detailed information about dosage is available in the following points. Taking into account these data, the 5 presentations of the echinocandins described below should be included in the WHO EML list as they help to correctly dose the drugs in the patient, avoiding economic losses.

6.1 Anidulafungin

- 100 mg of lyophilized powder for infusion (41,42).

6.2 Caspofungin (as acetate)

- 50 mg of powder concentrate for solution for infusion (43,44).
- 70 mg of powder concentrate for solution for infusion (43,44).

6.3 Micafungin (as sodium)

- 50 mg of powder for infusion (45,46).
- 100 mg of powder for infusion (41,45).

6.4 Dosing

The following dosing regimens were taken from treatment guidelines, FDA and European agencies approvals and package inserts. It has to be highlighted that treatment guidelines were reviewed and endorsed by different paediatric academies and societies including the American Academy of Paediatrics and the Paediatric Infectious Diseases Society and innumerable medical and infectious disease associations worldwide (17–20,41,43,46).

6.4.1 Adult patients

- **Anidulafungin**

The dosing of this echinocandin varies depending on the infection. For candidemia, intra-abdominal candidiasis (abscess) and peritonitis, patients should receive a single 200 mg loading dose followed by 100 mg/day thereafter of at least 14 days after the last positive culture. For oesophageal candidiasis, patients should take 100 mg on day one followed by 50 mg of anidulafungin for a minimum of 14 days and for at least 7 days after the symptoms resolution. The administration rate should not exceed 1.1 mg/min (18,20,41).

Patients weighting >120 Kg had similar outcomes than thinner ones with similar dosage. Thus, anidulafungin dosage regimens should be not adjusted in obese patients (up to 150 Kg)(47).

- **Caspofungin**

First day, a 70 mg loading dose followed by 50/mg day thereafter administered over an hour. In patients weighting 80 Kg or more, after the loading dose, a bigger dose of 70 mg of caspofungin in a day basis is recommended. No adjustment based on race or gender is necessary.

Dose correction is needed in obese patients. Pharmacokinetic studies showed a negative correlation between caspofungin concentration peak levels and body weight. Taken into consideration that caspofungin microbial effect is concentration dependent and that the area-under-concentration-time curve (AUC) of this echinocandin is lower in overweigh people than in thinner ones, caspofungin dose needs to be increased(48–

51). A 150 mg/day dose was recommended in this population with no adverse effect (no dose-limiting toxicity was reported) (52,53).

- **Micafungin**

Dosage regimen of this echinocandin varies from 50 to 150 mg/day depending on the indication. For prophylaxis of *Candida* infection the recommended dose is 50 mg/day while the dose should be augmented to 100 mg/day to treat acute disseminated candidiasis, *Candida* peritonitis and abscesses and to 150 mg/day for esophageal candidiasis (20,46).

Weight was associated with an increase in micafungin systemic clearance. Thus, dose adjustment should be performed for obese patients (54). Different reports showed that doses of 200 mg/day were efficient to treat *C. albicans* and *C. glabrata* infections in patients weighting up to 185 Kg (55). Using a simulation analysis, the following micafungin dosing formula was proposed: dose (mg) = patient weight (Kg) + 42 (rounding to the nearest 25 mg multiple). Using these dosing the AUC/MIC target was reached in more than the double of the patients when receiving micafungin in regular doses of 100 mg/day (56).

6.4.2 Paediatric patients

- **Anidulafungin**

Using data obtained from a paediatric phase I/II study where neutropenic children were treated with anidulafungin, no drug related adverse events were recorded in patients between 2 and 17 years which received doses of 0.75-1.5 mg/Kg. Plasma concentration corresponded to those obtained in adults following doses of 50-100 mg, respectively (57).

- **Caspofungin**

In patients aged between 3 month and 17 years, a 50 mg/m^2/day dose (with a loading dose of 70 mg/m^2/day not exceeding 70 mg/day) was selected. Similar (or slightly higher) exposures to adults were obtained (58). In neonates up to 3 months of postnatal age a dosage of 25 mg/m^2/day resulted in similar efficacy and exposure as 50

mg/m^2/day in older patients (59). Body surface should be obtained using Mosteller´s formula (60). Caspofungin is well tolerated in paediatric patients (22).

- **Micafungin**

As for adult patients, in pediatric population (2-17 years-old), dose varies depending on the infection to be treated. For invasive candidiasis, 2 mg/Kg is recommended (≤40 Kg of bodyweight) with a dose escalation option reaching 4 mg/Kg/day. For prophylaxis and oesophageal candidiasis a 1 mg/Kg and 3 mg/Kg (both for ≤40 Kg of bodyweight) regimens showed better results, respectively (61). Using pharmacokinetic modelling, simulations and data from a phase I study, it was suggested that a higher dose is required in neonatal and premature infants (> 1000 g) population. Doses between 10 mg/Kg to 15 mg/Kg were suggested due to relatively high frequency of secondary brain infections (62–64). In reality, the most commonly used micafungin dosage regimen in these populations are >4mg/Kg in neonates with invasive candidiasis (10 mg/Kg if central nervous system is involved) (65).

7 Whether listing is requested as an individual medicine or as representative of a pharmacological class.

- Pharmacological class under EML section 6.3 Antifungal medicines.

Micafungin should be selected as representative of the echinocandin class for the following reasons:

- It is registered in more countries.
- It has the simplest dose regimen.
- It is used and there is data supporting its use in chronic pulmonary aspergillosis, invasive aspergillosis and in neonates. This is not true for anidulafungin. The data supporting caspofungin as a treatment option of chronic pulmonary aspergillosis is very limited.
- It has less severe secondary effects.

However, caspofungin and anidulafungin should be considered as therapeutically equivalent alternatives.

8 Treatment details, public health relevance and evidence appraisal and synthesis.

8.1 Treatment details

(Requirements for diagnosis, treatment and monitoring).

8.1.1 Diagnosis

Since the beginning of this century, the challenges facing diagnostics in medical mycology included bigger populations of immunocompromised patients that are predisposed to be infected by a wider variety of fungi. Thus, the confirmation of the fungal etiology of an infection, followed by the identification of the causative agent and the evaluation of its sensitivity to antifungals is now mandatory. Specimens for fungal cultures and other relevant studies (wet mount, histopathology, serology, antigen detection, PCR, imaging) should be obtained before treatment to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Echinocandin Minimum inhibitory concentrations (MICs) are low for most *Candida* spp. including azole resistant species and strains harbouring mechanisms of resistance (secondary resistance) (33,34,38,39,66) . Antifungal susceptibility testing should be performed in any strain isolated from a normally sterile site but especially in the following cases:

- Isolates obtained from patients who have received prior treatment with an echinocandin drug (67).
- Isolates identified as *Candida glabrata* due to its higher rate of secondary resistance when compared with other *Candida* spp.(68).
- Species harbouring naturally occurring substitutions at echinocandin target (FKSp) show lower *in vitro* susceptibility as *Candida parapsilosis sensu lato* and *Candida guilliermondii* (69,70). This fact raises concerns about the response of these *Candida* spp. to these antifungals(20,71).

- *Candida auris* resistant mutants seem to be selected quickly. Repeated susceptibility testing should be performed since persistent and/or recurrent bloodstream infections due to this species have been documented (72,73).
- Echinocandin susceptibility testing can be carried out using standardized and commercially available microdilution and agar diffusion methods. The formers are described in different documents from recognized institutions such as the Clinical and Laboratory Standards Institute (CLSI) of the USA and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) of the European Union. These documents include all the testing procedures including media, inoculum preparation, incubation time, reading and interpreting results, and quality assessment. These documents are well known and widely accepted (74–81) .
    - Yeasts: Using the procedures described above, echinocandin MICs values for yeast vary between 10 dilutions (0.006 and 8.00 mg/L) allowing *FKS* mutants (the major mechanism of echinocandin resistance) to be distinguished(15,28,32,82). Species-specific clinical breakpoints and epidemiological cut off values have been established and are able to discriminate between susceptible and resistant and wild-type and non-wild-type strains, respectively(77,80,83).
    - Filamentous fungi: All filamentous fungi usually show very high echinocandin MIC values (most > 8 mg/L). It has been demonstrated that the detection of hyphae with morphological alterations is a better marker of in vitro susceptibility end point for echinocandins than MIC (16). The lowest drug concentration that produce these morphological alterations is defined as a 'minimum effective concentration (MEC)' and should be exclusively used for echinocandin susceptibility testing of moulds(76,79).
    - Which of the echinocandins should be tested *in vitro*? In 2013, caspofungin MIC values of more than 11,000 *Candida* spp. strains were evaluated using both European and American standardized methodologies and an important modal variability (wider MIC ranges) and truncated MIC distribution was reported. These issues were linked to caspofungin powder source, the quality of solvent

used for stock preparation and powder and stock storage conditions (length and temperature)(84). Later, it was suggested that anidulafungin or micafungin can be used interchangeably as surrogate marker for caspofungin susceptibility testing(35,85). These data induced the inclusion of a note in the reference protocols indicating that no epidemiological cut-off points for caspofungin were reported due to these result variabilities(74).

- Molecular- and proteomic-based methods for echinocandin susceptibility testing: The so-called whole-cell susceptibility testing using reference protocols need 24 to 48 h to obtain a trustworthy result(74–76,79). Thus, faster methods were proposed based on the claim that the detection of a *FKS* mutation (in its hot-spot regions) may predict a treatment failure equal to or more efficiently than an elevated echinocandin MIC(86). These methods include DNA-based methods as multiplex PCR (87,88), pyrosequencing (89), real-time PCR using different probes and melting curves (73,90,91), luminex-based methods (92), etc. and proteomic-based methods using MALDI-TOF (93,94). However, more data is needed to support its usefulness in real-life clinical setting. Some of these molecular-based susceptibility testing were specifically designed to be inexpensive and suitable to be applied in low-to-middle-income countries. As examples, we can state two classical PCR methods that cost < 5 dollars per sample. These methods are able to uncover mutations conferring echinocandin resistance in *C. glabrata* and in *C. albicans* (87,88). The former was successfully used to study a strain collection to uncover resistant strains (95).

8.2 Indications for echinocandins

(any) based on the full prescribing information (drug package inserts), clinical practice guidelines for the management of candidiasis and aspergillosis of the Infection Diseases Society of America, GEMICOMED-SEIMC/REIPI, and CDC (17–20,72).

In this section, the prescribing indications of the three approved echinocandins will be described. Many of the indications are defined in greater detail, more up-to-date and better classified in the treatment guidelines than in the drug inserts. For these reasons, the indications published by the manufacturers will be depicted in **Table 1** and the indications described in the treatment guidelines cited in the title of this section will be detailed later.

The definition of adult and paediatric populations showed slight differences in the drug inserts. In the anidulafungin package, paediatric patients are considered those aged between 1 month to less than 18 years-old while in the caspofungin insert, paediatric patients are those ranging from 3 months to 17 years of age. On the other hand, in the micafungin package, paediatric population include patients less than 16 years old. In all but micafungin, indications are the same for adults than for children. Anidulafungin is indicated for *Candida* infections (candidemia, intra-abdominal abscess and peritonitis) and for oesophageal candidiasis. Caspofungin is indicated for the treatment of invasive candidiasis, invasive aspergillosis refractory to the usual therapeutic dose and/or invasive aspergillosis in intolerant patients to amphotericin B and/or itraconazole (itraconazole was listed according with the regulators in 2001/2, prior to the licensure of voriconazole, posaconazole and isavuconazole). Refractory invasive aspergillosis was defined as the progression of the infection despite treatment or failure to improve in 7 day or more at the usual therapeutic dose. Caspofungin is also indicated in the drug insert for empirical therapy of candidiasis or aspergillosis in neutropenic febrile patients.

Micafungin package insert describes that it is indicated to treat invasive candidiasis and *Candida* infection prophylaxis in neutropenic patients (<500 neutrophils/µl for ≥ 10 days) both for adult and children. The indication for intravenous therapy of oesophageal candidiasis was only described for adults.

Table 1: Indications of the echinocandins (in alphabetical order: anidulafungin, caspofungin and micafungin) described in the package insert published by each manufacturer (Pfizer Inc., Merck and Co. Inc. and Astellas Pharma Tech Co. Ltd., respectively).

Drug	Adult	Paediatric

ANF[a]	*Candida* infections (candidemia, intra-abdominal abscess and peritonitis)	
	Esophageal candidiasis	
CSF [b]	Invasive candidiasis	
	Refractory invasive aspergillosis (defined as progression of the infection despite treatment or failure to improve in 7 day or more at the usual therapeutic dose)	
	Invasive aspergillosis in intolerant patient to amb, L-amb and/or itraconazole*	
	Empirical therapy of candidiasis or aspergillosis in neutropenic febrile patients	
MCF [c]	Invasive candidiasis	
	Oesophageal candidiasis where IV therapy is appropriate	Not indicated
	Candida infection prophylaxis in neutropenic patients (<500 neutrophils/µl) for ≥ 10 days.	
	Candida infection prophylaxis in patients going through an allogeneic haematopoietic stem cell transplantation.	

[a] Paediatric patients are considered those aged between 1 month to < 18 years.
[b] Patients between 3 months to 17 years of age are considered as paediatric population.
[c] Adults include adolescents ≥ 16 years of age and higher/ Children include neonates and adolescents < 16 years of age.
* Only itraconazole listed here as wording agreed with the regulators in 2001/2, prior to the licensure of voriconazole, posaconazole and isavuconazole.

The following list of indications summarize the data described in different treatment guidelines (17–20,72) . These prescription indications are for all three echinocandins and for adult and paediatric population, if otherwise is not stated:

- Prophylaxis of invasive candidiasis in the Intensive Care Unit setting.
- Empirical treatment of suspected fungal infection in febrile, neutropenic patients.
- Treatment of:
    - Candidemia in neutropenic and non-neutropenic patients.
    - Chronic disseminated (hepatosplenic) candidiasis.
    - Intra-abdominal candidiasis.

- *Candida* intravascular infections, including endocarditis and infections of implantable cardiac devices.
- *Candida* osteoarticular infections.
- Oesophageal candidiasis: For patients who cannot tolerate oral fluconazole.
- Infections caused by *Candida auris* and other multi-resistant species (considered the first option) (72).
- Invasive aspergillosis in haematological patients caused by voriconazole resistant *Aspergillus* spp. isolates (MIC >2 mg/L) in combination with voriconazole.

- Salvage therapy of:
  - Invasive pulmonary aspergillosis in ICU patients (combined with another antifungal agent).
  - Invasive aspergillosis in paediatric population (Caspofungin).
  - Chronic pulmonary aspergillosis in critically ill patients or those with azole resistance (micafungin or caspofungin).
  - Invasive aspergillosis in haematological patients (anidulafungin in combination with voriconazole).
  - Aspergillosis when amphotericin B (lipid formulations) and azoles cannot be used.

8.3 Therapeutic drug monitoring and drug-drug interactions affecting efficacy

Therapeutic drug monitoring (TDM) is encouraged for optimizing exposure to azole drugs (96–100), but is not required for the echinocandins. Echinocandins are structurally different molecules relative to azoles and have different distribution patterns. They have poor oral bioavailability requiring IV dosing. There have low urinary excretion and high protein binding. There is almost no hepatic metabolism (hydrolysis or chemical degradation) of these drugs and metabolites are eliminated via urine and faeces (101–104).

None of the echinocandins are substrates for cytochrome P450, thus few drug interactions occur. As for April 2019 and analysing more than 16,000 possible interactions, anidulafungin and micafungin were the antifungal drugs with the least interactions. Moreover, 10 of the few reported interactions were severe (and only with caspofungin), and none associated with sub-therapeutic echinocandin exposure (Table 2) (105,106).

The relation between echinocandin blood levels and treatment outcome is currently undefined, primarily because there is little inter-patient variation (67). Recent work demonstrated that the echinocandin drugs have limited penetration at the infection site (e.g. liver tissue) in patients with intra-abdominal candidiasis and could be the source of the emergence of resistant mutants (107). However, this issue could be avoided if the new generation of echinocandins such as rezafungin is used (107). Despite these last considerations, **echinocandin drug monitoring is not recommended**, whether to be used for prophylaxis or treatment (97,108). Moreover, no dosage adjustment is required for renal insufficiency and/or dialysis.

Table 2: Drug interactions with antifungals. Modified from (109).

Drugs		Type of drug-drug interaction (DDI)*				
		Severe	Moderate	Mild	Unlikely	Total
Azoles	Fluconazole	44	171	178	1093	1486
	Isavuconazole	50	81	22	1333	1486
	Itraconazole	134	158	112	1082	1486
	Posaconazole	91	189	142	1064	1486
	Voriconazole	140	179	140	1027	1486
Amphotericin B	Deoxycholate	19	125	88	1254	1486
	Liposomal	18	125	87	1256	1486
Echinocandins	Anidulafungin	0	0	3	1483	1486
	Caspofungin	10	38	13	1459	1486
	Micafungin	0	4	8	1474	1486
	Total	507	1080	809	13950	16346

*Numbers of licensed drugs interacting with the named antifungal. Severe: potentially life-threatening (ie severe toxicity of one drug or complete loss of activity). Moderate: dose adjustment possible to avoid major toxicity or loss of activity modest or small likelihood of significant (but not life-threatening) side effects. Mild: some change in drug exposure of one drug which does not need dose alteration and/or is unlikely to lead to any adverse events.

8.4 Dosing

Dosing regimens were described in the point 6.4 of this document.

9 Information supporting the public health relevance.

9.1 Epidemiological information on disease burden

A general lack of diagnostic capability limits the precision of all fungal disease estimates. Here we include only those fungal diseases for which echinocandins are useful. Unless otherwise stated, the data and estimates are summarized in Bongomin et al (2017) (4).

9.1.1 Candidaemia and invasive candidiasis

Blood culture is about 40% sensitive for invasive candidiasis, based on several autopsy and biomarker studies, which means that candidemia underestimates invasive candidiasis (6–8) . Despite these limitations, candidemia is one of the most common hospital-associated bloodstream infections. The overall burden of *Candida* spp. invasive infections remains as the fourth to the seventh cause of septicaemia worldwide for more than one and a half decade (110–122).. Candidaemia annual incidence has been documented in many countries. The incidence is lowest in very poor countries, Australia, New Zealand, Canada and northern Europe and highest in middle income countries such as India, Pakistan and Brazil. Population incidence rates vary from ~2/100,000 to 21/100,000 (Pakistan) (4). The global burden of candidaemia is therefore probably between 5 and 12/100,000 or 374,000 and 897,410 annual cases with a mortality ranging from 46 to 75%(2–5). The incidence of invasive candidiasis is probably 934,800 to 2,243,500 cases per year, based on the poor sensitivity of blood culture, not including oesophageal candidiasis which is not considered invasive.

The 4 major species of *Candida* causing invasive infection are *C. albicans* (40-60%), *C. tropicalis* (3-25%) (hotter climates), *C. parapsilosis* (~25%) (mostly nosocomial) and *C. glabrata* (~25%) (often a fluconazole super-infection). About 10 other species occasionally cause candidaemia, including *C. krusei* and *C. auris* (both showing intrinsic resistance to fluconazole). All species have isolates with secondary resistance to azole drugs and the rate of resistance vary among countries although the information is limited.

Invasive candidiasis is more common at the extremes of age – premature infants and older people. Diabetes, renal dysfunction and failure and antibiotic usage (number of classes and duration) are the main drivers, combined with immunocompromise, pancreatitis and intravascular catheters.

9.1.2 Intra-abdominal candidiasis

This name refers to a group of infections that include peritonitis, abdominal abscess and several other type of purulent infections after a perforation or leak of intestinal content into the peritoneal area. Clinical data on these Candida spp. infections is scarce (123,124). However, the prevalence of intra-abdominal candidiasis may reach the 40% of the patients with secondary or tertiary peritonitis (125–128). Diagnosis is difficult, there are no specific clinical signs and blood cultures are usually negative or it is hard to decide if a positive culture is due to a contamination (129). The main laboratory data that should be considered as an evidence for infection is a positive culture form a normally sterile site (intra-abdominal specimen obtained in an operation room) or obtained from a drainage device placed within 24 hours in patients with clinical evidence of infection (128). Considering these limitations, the estimated worldwide burden for these infections range between 60,000 to 100,000/cases/year (4) with an average global incidence of 1.15 cases/100,000 inhabitants (4.98/, 4.6/, 1.5/ and 1.4/100,000 in Mexico, Germany, Nigeria and Spain, respectively) (130–133).

9.1.3 Oesophageal candidiasis

Oesophageal and other mucocutaneous candidiasis is among the most common opportunistic infections in HIV patients and may be the first sign of HIV disease. These infections may produce incapacitating illness characterized by dysphagia, odynophagia and retrosternal pain and may serve as a focus of invasive disease (134–138).

About 20% of those HIV-infected people with CD4 counts <200/uL develop at least one episode of oesophageal candidiasis (139) and ~5% of those on antiretroviral therapy (ART)

(140). Using UNAIDS 2019 HIV estimates and assuming a 7-year decline to <200 CD4/uL in the 12,600,000 not on ART, a global total of 1,630,000 cases of oesophageal candidiasis is likely (65). In reality, it is probably higher than this as many of those on ART do not have their HIV disease controlled. It is very difficult to estimate the annual incidence outside HIV, but it probably doubles the global incidence. As in other *Candida* infections, *Candida albicans* is the most prevalent species implicated in oesophageal candidiasis (90%) but a more recent species diversification was produced (139,141–143). Initially, these infections respond to azole treatment. However, it is well known that they tend to recur in the absence of immune reconstitution (144). Hence, the actual standard of care is the chronic prophylaxis or intermittent therapy. Historically, amphotericin B was regarded as the treatment choice for azole unresponsive patients until the advent of echinocandins (145–148). Oesophageal candidiasis treatment with these echinocandin agents was found to be better than other therapies (**tables 3 to 5**).

9.1.4 Chronic disseminated candidiasis.

One of the associated syndromes in hematologic malignancy patients is Chronic disseminated candidiasis. This infection is relatively uncommon and as other *Candida* infections, *C. albicans* is the most commonly isolated organism followed by *C. tropicalis* and other azole-resistant or azole-less susceptible species as *C. krusei* and *C. glabrata*. Symptoms as fever and elevation of liver enzymes appear after the patient recovers from neutropenia (149–151). This is a relatively rare infection, but more common if antifungal prophylaxis is not routine in leukaemia patients.

9.1.5 Candida intravascular infections, endocarditis and infections of implantable cardiac devices.

Some conservative estimations consider that around 250,000 venous catheters/year are used in the UK and 300 million catheters/year are used per year in the US (3 million are venous catheters) (152). Intravascular devices (IVD)-related blood stream infections prevalence ranges from 0.5/1000 IVD-days to 2.7/1000 IVD-days depending on the catheter

type. These infections have bacterial and fungal etiology and *Candida* spp. is the forth in prevalence (153).

More than 70% of the cases of candidemia in non-neutropenic patients are related with the presence of intravascular devices as a central venous catheter (154–157). The implication of these devices on the development and persistence of *Candida* blood stream infections has been confirmed by the demonstration that catheter removal shorten the duration of candidemia and/or improved outcomes (158–162). These infections are tightly linked with the capability of *Candida* spp. to form biofilm over medical devices (163,164) and these infections are also named biofilm-related infections (165) . Echinocandins are active against biofilm formatting *Candida* spp. both *in vitro* and *in vivo* (166,167). This activity is related to the beta glucan content of the biofilm matrix, which is inhibited by echinocandins (168,169).

9.1.6 Invasive aspergillosis

Multiple patient groups are at risk of invasive aspergillosis, notably leukaemia and lymphoma, transplant recipients, lung cancer, advanced HIV disease and chronic obstructive pulmonary disease (COPD).

Invasive aspergillosis also occurs in intensive care (ICU) at about 5% (170)although a recent paper put this at 12% (171). It has recently been linked to influenza, 3% in hospitalized patients (172) and 8-23% in ventilated patients (170); and Covid-19 in severely ill patients (~20%) (173,174). Aspergillosis rates related with patients at ICU, with influenza or Covid-19 are difficult to estimate and so have been omitted from the estimates below.

The attack rate in acute myeloid leukaemia is at least 10%, and the number of cases in all other haematological conditions very similar (175) In 2017 there were ~120,000 AML cases globally (175), so a conservative estimate for all haematological patients is 24,000 but is probably higher and most are at risk (25). In 2018, there were an estimated 2,100,000 lung cancer cases. A large study from China indicated that 2.6% are complicated by invasive aspergillosis, a likely total of 54,600 (176).

There were an estimated 690,000 deaths from HIV in 2019 and ~4% are complicated by invasive aspergillosis (multiple studies)(177). This annual loss is about 27,600 cases of invasive aspergillosis, very few currently diagnosed.

There are 3 estimates of invasive aspergillosis complicating COPD admissions to hospital – 1.3%, 1.9-2.7% (depending on definition) and 3.9%; the first from Madrid, the latter 2 from different cities in China (178). A recent re-assessment of the prevalence of GOLD stage II-IV COPD concluded that there are about 552 million affected globally and a conservative estimate of 10.5% are admitted to hospital each year. This puts the annual incidence of invasive aspergillosis complicating COPD at 753,900 to 2,261,700. Many of these diagnoses are not currently made.

9.1.7 Chronic pulmonary aspergillosis

By means of UK prospectively collected data from the late 1960's using chest radiographs and 2005 global and country pulmonary TB data, the annual incidence and 5-year period prevalence of chronic pulmonary aspergillosis (CPA) was estimated at 372,000 and 1,174,000 (with wide sensitivity bounds) (179). This estimate was related only to survivors of pulmonary TB, 1-4 years after completing anti-TB therapy. A recent prospective study from Gulu, Uganda 2 to 7 years after completing anti-Tuberculosis (TB) found an equal number of CPA cases in HIV positive and negative people (180). The annual rate of development of CPA in those with cavitation on chest radiograph was 6.5% but 0.2% in those without cavitation, consistent with the UK data.

In a work just published from Indonesia, 13% were found to have CPA as they finish their anti-TB therapy (181) and 9% in Uganda had serological markers of CPA at the end of TB therapy (182) Longer follow is required. Some of these patients would survive to be included in the studies addressing CPA moths or years after TB and some would not. If translated into Indonesia alone (650,000 survivors), this would equate to an annual incidence of 84,500, and a 5 year period prevalence of >200,000.

A cross-sectional study in Lagos, Nigeria with an insensitive *Aspergillus* antibody assay in HIV negative patients treated for TB but smear and GenXpert negative found a 19% prevalence of CPA In the whole study (HIV positive and negative, GeneXpert positive and negative) 8.2% had CPA (183). These data translates into about 142,000 5-year prevalence in Nigeria in TB survivors.

Almost all (>90%) of CPA patients have underlying pulmonary disease. TB and COPD are the most common. Pneumothorax, prior lung cancer resection, rheumatoid arthritis, asthma are the next most frequent. A separate study in those with fibrocystic sarcoidosis found a global total of ~72,000 cases, using a 5% prevalence rate among the 1.2 million affected worldwide (184).

The global estimate of CPA is therefore certainly more than 2 million and may be as high as 4 million – so the usual quoted figure is 3 million.

9.2 Assessment of current use

Echinocandins as a class of drugs are currently used as prophylaxis of *Candida* infections in haematopoietic stem cell transplant recipients and empirical therapy during neutropenia, especially in those receiving vincristine because of drug interactions with azoles. They are considered first option of treatment for proven candidemia, acute disseminated candidiasis and *Candida* peritonitis and abscesses (20). In addition, echinocandins are a treatment option for oesophageal candidiasis to reduce the risk of relapses in HIV patients (185) , with the possible addition of oral suppressive therapy. Turning to aspergillosis, these drugs are used for the treatment of invasive aspergillosis refractory to other treatments or where voriconazole cannot be used because of drug interactions or toxicity (17,186). They have also been recommended in combination with an *Aspergillus* active azole when azole resistance is strongly suspected or documented (187).

Table 3. Clinical indications and regimens of Anidulafungin for adults

Diagnosis	Daily doses and length of treatment
Candidemia, intra-abdominal abscess and peritonitis	Loading dose (day 1): 200 mg Anidulafungin Day 2 and thereafter: 100 mg Anidulafungin Duration: Depends on patient´s clinical response. Treatment should continue for ≥14 days after the last positive culture.
Oesophageal Candidiasis	Loading dose (day 1): 100 mg. Day 2 and thereafter: 50 mg. Duration: minimum 14 days and at least 7 days after symptoms resolution. There are risks of relapse in HIV patients. Thus, oral suppressive therapy should be considered.

Table 4. Clinical indications and regimens of Caspofungin for adults

Diagnosis	Doses and length of treatment
Empirical therapy during neutropenia	Loading dose (day 1): 70 mg Day 2 and thereafter: 50 mg* Duration: Depends on patient´s clinical response. It should be continued until neutropenia resolution.
Candidemia and other *Candida* infections	Loading dose (day 1): 70 mg. Day 2 and thereafter: 50 mg*. Duration: minimum 14 days and at least 14 days after the last positive culture. This length may vary if the patient is persistently neutropenic. In these cases, the therapy should be prolonged until the resolution of the neutropenia.

Oesophageal candidiasis	50 mg*. There are risks of relapse in HIV patients. Thus, oral suppressive therapy should be considered.
Invasive aspergillosis refractory to other treatments as voriconazole.	Loading dose (day 1): 70 mg. Day 2 and thereafter: 50 mg*. Duration of treatment depends on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

* If the 50-mg dose is well tolerated but with no adequate clinical response, the daily dose can be increased to 70 mg (Although increase in efficacy with this higher dose has not been demonstrated). This dose increase is usually well tolerated (based on limited safety data).

Table 5. Clinical indications and regimens of Micafungin for adults

Diagnosis	Daily doses and length of treatment
Candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses	100 mg*. Mean duration in patients treated successfully: 15 days (range 10-47 days).
Oesophageal candidiasis	150 mg*. Mean duration in patients treated successfully: 15 days (range 10-30 days)
Prophylaxis of *Candida* infections in Haemtopoietic Stem Cell Transplant recipients	50 mg*. Mean duration in patients who experience success prophylactic therapy: 19 days (range 6-51 days)

*No loading dose required

9.2.1 Use in Special Populations

9.2.1.1 Race and Gender

No differences were seen among races. The same dose of echinocandin produce a greater AUC (area under the curve) in women than in men, due to body weight differences.

9.2.1.2 Paediatric

A detailed description of dosing and treatment regimen was already depicted in section 5.4.2.

9.2.1.3 Elderly

Plasma concentrations of the three echinocandin drugs increase slightly with age. However, no dosage adjustment is necessary for this population for any of the three approved echinocandin drugs. However, no overall differences in safety and effectiveness were observed between old and younger subjects.

9.2.1.4 Pregnancy

The effect of echinocandins in pregnant women or nursing infants are not well studied (no adequate and well-controlled studies). Visceral abnormalities and increased abortion were reported using animal models (rabbits). These drugs should be used during pregnancy or during breast-feeding only if the benefit justifies the potential risk. [Note azole therapy is specifically cautioned against as increased risk of foetal abnormality. Amphotericin B is probably safe in pregnancy].

9.2.1.5 Disadvantaged populations

In most parts of the world, the population that would use these drugs includes people living with HIV who suffer accompanying fungal infections. These patients are usually members of one of the many vulnerable groups including intravenous drug abusers, sex workers, prisoners and those living in urban poverty.

Anidulafungin dosage adjustments are not required based on HIV status, irrespective of concomitant anti-retroviral therapy.

9.2.1.6 Renal Insufficiency

Dosage adjustments are not required for patients with any degree of renal insufficiency including those on haemodialysis. Echinocandins are not dialyzable thus supplementary dosing is not required following haemodialysis.

9.2.1.7 Hepatic impairment

For anidulafungin and micafungin no dosing adjustments are required for patients with any degree of hepatic insufficiency, since no important concentration differences were observed specially for subjects with mild to moderate hepatic insufficiency (Child-Pugh class A or B). A slight decrease in AUC for anidulafungin was observed in patients with more significant hepatic dysfunction (class C). However, this reduction was within the range of population of healthy subjects.

On the other hand, caspofungin plasma concentration in subjects with mild and moderate hepatic insufficiency was increased when compared with healthy individuals. However, a dosage reduction is only recommended in subjects with Child-Pugh score between 7 and 9 (moderate insufficiency). There is no sufficient clinical experience in patients with severe hepatic insufficiency (Child-Pugh > 9).

9.3 Target populations

As described before, populations in which echinocandins should be used include: patients suffering different haematological malignancies, solid cancers, hematopoietic stem cell transplant recipients, neutropenic febrile patients, patients with CVC associated infections, HIV patients and other immunosuppressed patients, as well as those with serious chronic pulmonary aspergillosis (17,19,20).

9.4 Likely impact of treatment of the disease

9.4.1 Prophylaxis of *Candida* infections in haematological malignancy and in Haematopoietic Stem Cell Transplant recipients.

The incidence of most hematologic malignancies increases with age. Aging of the population is a fact and an increase in the number of hematologic malignancies is alarming (175,188–190). Antifungal prophylaxis is the standard of care for haematological malignancy or hematopoietic cell transplantation patients (191–193). A significant reduction in invasive fungal infections and mortality was seen when azole drugs were used for prophylaxis. However, azole drugs are associated with a range of complications as breakthrough infections, drug interactions, toxicities and inter-patient concentration variabilities. These facts are particularly important in patients receiving intensive chemotherapy for haematological malignancy or those hematopoietic cell transplanted recipients. In these types of patients, echinocandins became a good prophylaxis option for *Candida* infections due to its safety and its wide range of action (most *Candida* spp. including naturally azole resistant species). Moreover, echinocandins have clinical activity against some filamentous fungi as *Aspergillus* spp.) (**tables 12 and 13**).

9.4.2 Empirical therapy for neutropenic febrile patients.

Persistent fever in neutropenic patients receiving antibacterials can be produced by an invasive fungal infection. These infections are difficult to detect soon enough to correctly intervene (8). Thus, empirical therapy is the standard of care for neutropenic febrile patients. Early studies demonstrated that amphotericin B (deoxycholate and liposomal) reduce morbidity and mortality associated with unresponsive febrile patients under antibacterial treatment (23,194–196). Response rate was 16% higher in amphotericin B treated group when compared with untreated. This better rate means that only 1 of 68 (1.5%) patients developed a fungal infection in the first group compared with 6/64 (9.4%) patients in the second (196). Empirical treatment was firstly shifted to extended-spectrum azoles in order to reduce polyenes toxicities with at least the same clinical success (197–199). More recently, echinocandins became the drugs of choice due to their safety and

ability to prevent azole breakthrough infections without an inferiority to azoles and/or amphotericin B (200,201).

9.4.3 Deep-seated Candida infections as acute disseminated candidiasis, *Candida* peritonitis and abscesses.

The mortality rate for candidemia varies between 23 and 65% (23.7%, 33.7%, 43.3% and 62.1% after 7-, 14-, 30- and 365-days of follow up after candidemia diagnosis) (2,202,203). The rate of candidemia-related deaths is reduced if an echinocandin is chosen as primary treatment instead of azole drugs (for *Candida glabrata* and *Candida krusei* 41.5 vs 50.9 and for *Candida albicans* and *Candida tropicalis* infections 38.6 vs 58.0, respectively) (203,204) (**Tables 7 to 9**).

9.4.4 Oesophageal candidiasis

As more than 30% of the HIV/AIDS patients suffer from oesophageal candidiasis, effective therapy is important to minimise weight loss (205,206). The current initial treatment of this deep mycosis includes oral azoles. Azole resistance is seen in 3-7% of *C. albicans* isolates and clinical failure is difficult to manage in these patients. The high relapse rate (near 100%) made the use of an echinocandin mandatory as chronic prophylaxis or intermittent therapy for azole-irresponsive patients. The overall response rate (by endoscopic examination) mean is 82.7% (ranging from 68.8 - 97.2% depending on the used echinocandin and the dose) (207–209) (**Table 6**).

9.4.5 Invasive aspergillosis refractory to azole and amphotericin B treatment or intolerance to these antifungal agents.

Invasive aspergillosis mortality without antifungal treatment is 100% and 40-50% respond to itraconazole and voriconazole treatments, respectively. Some of this unresponsive rate is due to azole secondary resistance (or intrinsic resistance in some cryptic species). Echinocandins (micafungin or caspofungin) were proposed as salvage therapy in settings in which polyene and azole antifungals are contraindicated for toxicity and/or resistance. However, this recommendation is classified as weak and it is based on moderate-quality evidence (210) (**Table 13**).

10 Review of benefits: summary of evidence of comparative effectiveness.

10.1 Identification of clinical evidence

(search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Caspofungin was the first echinocandin approved by FDA (2001), followed by micafungin (2005) and anidulafungin (2006) (211). However, clinical studies were conducted since 1995 (212,213), 2004 (214) and 2000 (212,215), respectively. Micafungin was approved in Japan, following clinical studies there, in 2002. The authors of this application have extensive experience studying echinocandins. They have participated in molecular studies of its targets, its molecular mechanisms of resistance, *in vitro* antifungal susceptibility testing, experimental *in vivo* treatments, patient treatments, clinical trials and grants writing and reviewing. As of March 2, 2020, there are 4,072 papers listed on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) using "echinocandins" as keyword. Out of these papers, 179 are echinocandin ´clinical trials´ or meta-analysis and 809 are reviews were ´echinocandins´ are the main topic or at list mentioned on their list of keywords. Moreover, more than 25% of the papers (1184/4072) were published in the last 5 years.

10.2 Summary of available data for echinocandins

(appraisal of quality, outcome measures, summary of results)

Echinocandins were developed based on the first cyclic lipopeptides reported in 1974 and 1985 named Echinocandin B and pneumocandin B_0, respectively (216). It took almost a decade to enter caspofungin (the first approved echinocandin) into clinical development in 1995 (216). Echinocandin development programs were planned to prove its tolerability, safety and efficacy in *Candida* spp. and *Aspergillus* spp. infections in comparison to the standard of care at that time (amphotericin B and fluconazole). Some difficulties were encountered during the initial clinical trials as difficulties in the diagnosis, the evaluation of outcome in severe fungal infections and the high risk of mortality if the drug in study is not

effective. In real-life clinical practice, treatment is often empirical and the requirement of invasive procedures in severely ill patients pose a high risk making a definitive diagnosis and endpoint determination difficult. Most of these issues were circumvented by the first studies of caspofungin usefulness evaluation and then done for the other two approved drugs of the class. These studies were conducted for the evaluation of the treatment of oesophageal candidiasis where the risk of treatment efficacy evaluation was relatively low (endoscopy and/or biopsy), the high number of patients who could be enrolled (common infection in AIDS population), high morbidity and recurrence after fluconazole treatment, etc. (145,217).

10.3 Summary of available estimates of comparative effectiveness for echinocandins

Several treatment outcomes studies are summarized in the subsequent tables (tables 9 to 16). A summary of the data depicted in tables (with a conclusion) was included under each of the table titles. Tables are intended as summaries of the main published data on echinocandin effectiveness in different clinical settings. As general conclusions of all the analysed data it can be stated that:

Echinocandins are better or at least as efficient as different comparators for all the described *Candida* infections including oesophageal candidiasis, candidemia, different forms of invasive candidiasis and infections caused by different *Candida* species. Moreover, same good results were obtained for echinocandins as treatment options in the paediatric population and as prophylaxis and empiric therapy of invasive candidiasis in different immunosuppressed populations.

Echinocandins are recommended as salvage therapy for aspergillosis refractory to approved therapy (amphotericin B and *Aspergillus* active azole agents).

Table 6: Effectiveness of echinocandins in clinical trials for oesophageal candidiasis.

Effectiveness of echinocandins was firstly evaluated in oesophageal candidiasis patients. This population was chosen because there was an objective way to evaluate treatment efficacy using the endoscopic cure rate and a relatively big population of patients with similar symptoms was available. In all the following studies cure rate and safety profile were similar or better than treatments with comparator drugs (amphotericin B or fluconazole).

Disease	Refs	Type of study	Number of patients	Treatment	Outcome
Oesophageal candidiasis	(145)	Randomized double-blind study	128	46 patients: 50 mg CSF/day. 28 patients: 70 mg/CSF/day. 54 patients: 0.5 mg/Kg AMB	Endoscopic cure rate was dose dependent. 74% for 50mg/day and 89% using 70mg/day. With both doses, the cure rate was higher than for AMB. CSF was safer.
	(148)	Randomized, double-blind, double-dummy study	601/494 finished the study	IV ANF (100 mg on day 1, followed by 50 mg/day) or oral FLC (200 mg on day 1, followed by 100 mg/day) for 7 days beyond resolution of symptoms (range, 14-21 days).	Rate of endoscopic success for ANF (242/249 [97.2%]) and for FLC (252/255 [98.8%]). Similar safety profile.

	(147)	Randomized, double-blind, parallel-group, dose-response study	245 HIV+ patients	MCF (50, 100, or 150 mg per day) or FLC (200 mg per day). Both IV for 14-21 days.	Endoscopic cure rate was dose-dependent for MCF: 68.8% (50 mg/d), 77.4% (100 mg/d) and 89.8% (150 mg/d). MCF doses ≥ 100mg/day efficiency was comparable to FLC 200 mg (86.7%). Similar safety profile.

ANF: anidulafungin, CSF: caspofungin, MCF: micafungin and FLC: fluconazole, IV: intravenous.

Table 7: Usefulness of echinocandins in clinical trials for candidemia and common forms of invasive candidiasis.

The following group of clinical trials highlight the effectiveness of echinocandins when compared with amphotericin B in terms security and efficacy since all echinocandins were at least as good as amphotericin B. When fluconazole was used as comparator, anidulafungin showed better response rate for all *Candida* spp. but *C. parapsilosis sensu lato*. This last point showed for the first time that some *Candida* spp. would behave differently.

Disease	Refs	Type of study	Number of patients	Treatment	Outcome
Candidemia and invasive candidiasis	(218)	Randomized double-blind study	224	114 patients: 70 mg loading dose + 50 mg/day CSF 125 patients: 0.6-0.7 mg/Kg AMB (non-neutropenic) 0.7-1.0 mg/Kg AMB (Neutropenic)	Resolution of all symptoms and signs of *Candida* infection and culture-confirmed eradication. 80.7% CSF vs 64.9% AMB. CSF safer than AMB.
	(219)	randomized, double-blind, non-inferiority trial	245	ANF: 127 patients 200 mg loading dose and 100 mg/day. FLC: 118 patients 800 mg day 1 followed by 400 mg/day.	Better microbiological and global response for ANF group (88 and 77%) than for FLC group (76 and 61%) for all *Candida* spp. Better microbiological and global response in FLC group than in ANF group for *C. parapsilosis* sensu lato (64% vs 83%)

	(220)	double-blind, randomized, multinational non-inferiority study	392	202 patients: MCF (100 mg/day) 190 patients: LAMB (3 mg/Kg per day)	Treatment success: 181 (89·6%) patients treated with MCF and 170 (89·5%) patients treated with LAMB.
	(221)	international, randomized, double-blind trial	578	MCF 100 mg: 191 patients. MCF 150 mg: 199 patients. CSF 50 mg: 188 patients.	MCF 100mg and 150 mg: Successful for 76.4% and 71.4%, respectively. CSF 50 mg: 72.3% success. No need to increase MCF dosage and similar success with both echinocandins
	(25)	prospective, randomized, double-blind study	120	CSF 70 mg on day 1 plus 50 mg/day: 60 patients. MCF 150 mg: 60 patients	CSF and MCF showed similar adverse events (5% and 10%, respectively) and similar overall response rates were obtained for oesophageal candidiasis, invasive candidiasis and chronic pulmonary aspergillosis.

ANF: anidulafungin, CSF: caspofungin, MCF: micafungin and FLC: fluconazole, LAMB: liposomal amphotericin B.

Table 8: Clinical trials evaluating the echinocandins activity against less common forms of invasive candidiasis.

This clinical trial showed that the efficacy of caspofungin in uncommon infections is similar to the observed effectiveness for candidemia. Higher doses were well tolerated.

Disease	Refs	Type of study	Number of patients	Treatment	Outcome
Endocarditis, osteomyelitis, peritonitis, chronic-disseminated and septic arthritis caused by *Candida* spp.	(176)	Multicenter comparative study using CSF as primary or salvage monotherapy.	48 (adults with non-bloodstream *Candida* spp. infections)	CSF: 70 mg loading dose. 50 mg/day. 100 mg/day for endocarditis, osteomyelitis or septic arthritis. 150 mg/day for inadequate responses.	Overall success rate: 81%. Endocarditis: 33% (1/3). Osteomyelitis and arthritis: 100 %. Overall 12 weeks mortality: 23%. Elevated dosage (100-150 mg/day) was well tolerated.

CSF: caspofungin.

Table 9: Effectiveness of echinocandins in clinical trials for *Candida* spp. different than *Candida albicans* (non-*albicans Candida* spp.) infections.

Some *Candida* spp. show intrinsic high echinocandin (222) and azole MIC values (20). The clinical trials depicted in the following tables studied the efficacy of echinocandins against such species. As a good example it should be mentioned one of the first clinical trials showing that infections with the species of the *C. parapsilosis* complex responded better to fluconazole than to echinocandin treatment (222), or that *C. krusei* or *C. glabrata* infections had few treatment options. Thus, it was mandatory to evaluate the effectiveness of echinocandins in patients infected with these species. The data summarized in the table demonstrate that echinocandins showed similar response rates than other classes of antifungal agents independently of the *Candida* species causing the infection. It has to be highlighted that most of the infectious agents were *C. tropicalis*, *C. parapsilosis sensu lato*, *C. glabrata sensu lato* and *C. krusei* and no identification to the level of cryptic species were reported in any of these trials.

Disease	Refs	Type of study	Number of patients	Treatment	Outcome
Non-*candida albicans* infections	(223)	Meta-analysis reviewing CSF producer database (5 clinical trials)	379 patients: 212 (with common non-*albicans*) and 167 (with *C. albicans*). Non-a*lbicans* species were mostly *C. parapsilosis*, *C. tropicalis* and *C. glabrata*.	74% and 72% received 50 mg CSF and the rest ≥ 100 mg CSF. For non-*albicans* and *C. albicans* infections (respectively)	Positive response rates in the range of infections with *C. albicans* (at least 70%). Better results for *C. glabrata* (>85%).

	(224)	Pooled randomized trials of MCF vs comparator.	183 patients: 144 infected with *C. glabrata* and 39 with *C. krusei*.	117 patients received MCF 100 or 150 mg/day.	Similar cure rates and mortality were observed for both MCF treated patients and comparator.
	(225)	Pooled randomized trials of MCF vs CSF and MCF vs. L-AMB.	1072 patients. Non-*albicans* species were mostly *C. tropicalis*, *C. parapsilosis sensu lato*, *C. glabrata* and *C. krusei*.	MCF 100 mg/day (n=438) vs. L-AMB 3 mg/Kg (n=247). MCF 150 mg/day (n=199) vs. CSF 70 mg on day 1 followed by 50 mg/day (n=188).	MCF, CSF and L-AMB exhibit good treatment response rates despite the *Candida* spp. that is infecting.

CSF: caspofungin. MCF: micafungin. L-AMB: liposomal amphotericin B.

Table 10: Effectiveness of echinocandins in paediatric population clinical trials (*Candida* spp. and *Aspergillus* spp. infections).

Data about the pharmacokinetics and safety of echinocandins in paediatric population was scant. The following table describe the main clinical trials showing the effectiveness of these drugs in children. Moreover, different doses were tested in order to establish the correct treatment regimen. No adverse effects were seen, good therapeutic results were obtained and these drugs in children showed similar pharmacokinetic profiles to those of adult patients.

Disease	Refs	Type of study	Number of patients	Treatment	Outcome
Empirical treatment for neutropenic paediatric patients with high risk of invasive mycoses	(57)	A multicentre, open-label, ascending-dosage study to assess pharmacokinetics and safety of ANF	24.	0.75 or 1.5 mg ANF/Kg of weight	ANF 0.75 – 1.5 mg/Kg show similar pharmacokinetics than adults receiving 50-100 mg/day. ANF was well tolerated. No drug related serious adverse events were observed.
Candidemia and other forms of invasive candidiasis in paediatrics	(226)	Double-blind, randomized multinational trial.	98 (MCF group: 48 and LAMB group: 50).	MCF (2 mg/Kg) vs. LAMB (3 mg/Kg) as first-line treatment.	Treatment success for MCF: 72.9% and 76% for LAMB. Similar efficacy and safety.

Deep seated mycoses in paediatric population (salvage)	(227)	multicenter, prospective, open-label study	48 proven mycoses: 10 Invasive aspergillosis; 37 invasive candidiasis; 1 oesophageal candidiasis. Age range: <2 to 17 years old.	CSF 50 mg/m2 per day (based on body surface area; maximum: 70 mg/day) after a 70-mg/m2 loading dose on day 1.	Good results were achieved in 50% of invasive aspergillosis patients, in 81.1% of invasive candidiasis and in the oesophageal candidiasis patient. Therapy success was similar to the results obtained for adults with these infections. No drug-related adverse effects were seen.

ANF: anidulafungin, CSF: caspofungin, MCF: micafungin and FLC: fluconazole, LAMB: liposomal amphotericin B.

Table 11: Clinical trials evaluating the effectiveness of echinocandins for prophylaxis of invasive candidiasis in different immunosuppressed populations.

Invasive fungal infections are one of the most common cause of morbidity and mortality in immunosuppressed patients. Antifungal prophylaxis is an important tool to reduce the burden of these infections. The following clinical studies compared the usefulness of echinocandins vs different comparators. Echinocandin provide similar results than azole for prophylaxis.

Disease	Refs	Type of study	Number of patients	Treatment	Outcome
Prophylaxis of invasive candidiasis in haematopoietic stem cell transplantation.	(228)	Phase III randomized, double blind. MCF vs. FLC for prophylaxis of invasive candidiasis-	882 (425 received MCF and 457 FLC).	50 mg/day MCF (or 1 mg/Kg) and 400 mg/day FLC (or 8 mg/Kg)	Overall efficacy for MCF 80% and for FLC 73.5%. Breakthrough infections: 7 in MCF arm and 11 in FLC arm (4 and 2 candidemias, respectively). MCF was licensed for prophylaxis of invasive *Candida* infections in allogeneic HSCT patients based on the results of this trial.
Prophylaxis in patients with	(229)	Randomized, Open label	192 patients in induction chemotherapy for acute	50 mg/day CSF and 200 mg/day IV-ITC	99 patients completed the antifungal prophylaxis without a fungal infection (51% ITC and 52% CSF). 5 patients in the ITC arm developed fungal infections (4 *Candida* spp. and 1 Aspergillus spp.) and seven in

haematologic malignancies			myelogenous leukemia or myelodysplastic syndrome (86 IV-ITC and 106 CSF)		the CSF group (2 candidemia, 2 *Aspergillus* spp., 2 *Trichosporon* spp. and 1 *Fusarium* spp.). Both treatments were well tolerated.
Prophylaxis of invasive candidiasis in stem cell transplant recipients	(230)	Retrospective medical record review	123	CSF 50 mg/day (104 patients) CSF 35 mg/day (19 patients)	Nine patients (7.3%) developed breakthrough invasive fungal infections: *Candida* spp. (n=2), *Aspergillus* spp. (n=3), *Exserohilum* sp. (n=1), one unspecified mould and two echinocandin intrinsically resistant isolates (*Rhizopus* sp. and *Cryptococcus* sp.).
Prophylaxis of invasive candidiasis in liver transplant recipients	(231)	Prospective, multicenter, non-comparative, open-label trial	71	CSF, 70 mg loading dose followed by 50 mg/day. For at least 21 days.	Observation period spanned 100 days. Two patients developed breakthrough fungal infection (wound infection): *Mucor* spp. (echinocandin intrinsically resistant) and *C. albicans.*

ANF: anidulafungin, CSF: caspofungin, MCF: micafungin and FLC: fluconazole. IV-ITC: intravenous itraconazole.

Table 12: Clinical trials where echinocandins as (first line treatment) efficacy was evaluated against aspergillosis.

Azoles are the drug of choice to treat invasive aspergillosis. This mycosis is a common complication in haemtopoietic stem cell transplantation recipients. In these patients is difficult to keep an equilibrium between efficacy and toxicity when using regular antifungal treatments. Thus, echinocandins were seen as a plausible therapeutic option. The clinical trials shown in the following table were designed to test echinocandin efficacy and safety to treat invasive aspergillosis. The success rate was low when caspofungin was used but the results were better for micafungin when using voriconazole as comparator. However, based on these trials, echinocandins are not recommended in treatment guidelines as primary monotherapy for the treatment of invasive aspergillosis.

Disease	References	Type of study	Number of patients	Treatment	Outcome
Invasive aspergillosis in allogeneic haematopoietic stem cell transplant patients	(232)	Phase II, open-label, non-randomized, multicentre study	24	CSF: 70 mg loading dose and 50 mg/day. Doses modifications: for patients weighting >80 Kg (70 mg/day) or with moderated hepatic insufficiency (70 mg loading dose and 35 mg/day)	12-week survival of 50%. *
	(233)	Phase II, open label, non-comparative, multicentre study	61	CSF: 70 mg loading dose and 50 mg/day.	Success rate 33% (20/61). *

				Doses modifications: for patients weighting >80 Kg (70 mg/day) or with moderated hepatic insufficiency (70 mg loading dose and 35 mg/day)	
	(234)	Randomized, multicentre, open-label trial comparing MCF vs VRC (both intravenous)	97 (50 in MCF arm)	MCF: 150 - 300 mg/day. Dose of MCF was not fixed because there was no data available about the dose effect of MCF in the treatment of pulmonary aspergillosis.	No significant differences in efficacy rate between arms (68.0% for MCF vs. 58.7% VRC). In the safety evaluation, significant less adverse events occurred in the MCF group.

*Based on these two studies, echinocandin is not recommended as primary therapy (monotherapy) for the treatment of invasive aspergillosis.

CSF: caspofungin, MCF: micafungin VRC: voriconazole.

Table 13: Efficacy or echinocandins against aspergillosis refractory to approved therapy (salvage therapy).

Invasive aspergillosis is associated with frequent treatment failures. The mortality is worse for refractory infections specially when the antifungal is switched to a salvage monotherapy (222). The trials described in the following table were aimed to assess the efficacy of echinocandins as salvage therapy for aspergillosis.

Disease	References	Type of study	Number of patients	Treatment	Outcome
Acute aspergillosis in a wide variety of patients	(186)	Multinational, non-comparative, open-label study	Total: 225. MCF as primary treatment: 29 (12 alone and 17 in combination). MCF as salvage (for toxicity or refractory): 196 (22 alone and 174 in combination)	MCF alone: 75 mg/day (1.5 mg/Kg/day for patients < 40 Kg). Doses were increased in 75 mg increments (if well tolerated) until 200 mg or 225 for European and non-European patients, respectively. MCF in combination	0% (0/12) and 50% (6/12) complete and partial response when MCF used alone as primary therapy, respectively. Complete and partial response of 11.8% and 17.6% when used in combination, respectively. Complete and partial response: 7.5% (13/174) and 27% (47/174) complete and partial response when MCF used in combination for

					refractory aspergillosis, respectively. Complete and partial response of 13.6% (3/22) and 27.3% (6/22) when used alone for refractory aspergillosis, respectively.
	(235)	Multicentre, open-label, non-comparative	53 (37 CSF+triazole and 16 CSF+AMB)	CSF (50 mg daily, after a 70-mg loading dose) plus a triazole (ITC or VRC) or plus AMB (deoxycholate or Lipid)	55% (29/53) patients had a favourable response (25 partial and 4 complete)
	(236)	Prospective, Multicentre, Observational Study	87 (47 received LAMB and 40 CSF+VRC)	Combination arm CSF (70 mg loading dose and 50 mg/day plus VRC 6 mg/Kg/12 h followed by 4 mg/Kg/12 h. Comparator: LAMB	90 days survival: 67.5% (27/40) for CSF+VRC and 51% (24/47) for LAMB. In patients with renal failure and those with *A. fumigatus* CSF+VRC was statistically linked with

					better improvement at 90-day (multivariate analysis)
Invasive aspergillosis refractory to approved treatments	(237)	Multicentre, non-comparative	98 (83 refractory).	MCF alone: 8. MCF plus another antifungal drug: 90. MCF alone: 75 mg/day (1.5 mg/Kg/day for patients < 40 Kg). Doses were increased in 75 mg increments (if well tolerated)	Response was seen in 24% (22/90) in refractory patients when combination treatment was used. When MCF was used alone a 38% of positive response was seen.

CSF: caspofungin, MCF: micafungin, ITC: itraconazole, VRC: voriconazole, AMB: amphotericin B, LAMB: lipid amphotericin B.

11 Review of harms and toxicity: summary of evidence of safety.

11.1 Echinocandin recommendations in guidelines

Echinocandins has been recommended as first treatment option for *Candida* spp. infections and as salvage or in combination with other antifungals for *Aspergillus* spp. infections in different guidelines (18,20,210). These guidelines were published by European and/or North American infectious diseases societies and endorsed by different South American and Asian societies becoming, without discussion, the treatments of choice or the standard of care that should be met or aspired to.

The methodology used to establish the quality of the evidence in the guidelines is explained below in **figure 1** and **Table 14**, respectively. The recommendations for the different infections types and populations are shown in **table 15** including recommended doses, quality of evidence, comparators and conclusions. In all guidelines, echinocandins are considered the first treatment option for initial therapy for candidemia (in any population), for chronic disseminated candidiasis (hepatosplenic), for suppurative thrombophlebitis and for oropharyngeal candidiasis refractory to fluconazole. Moreover, this class was suggested as the better option for Prophylaxis and to Prevent Invasive Candidiasis in intensive care units.

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology (unrestricted use of the figure granted by the US GRADE Network) (222).

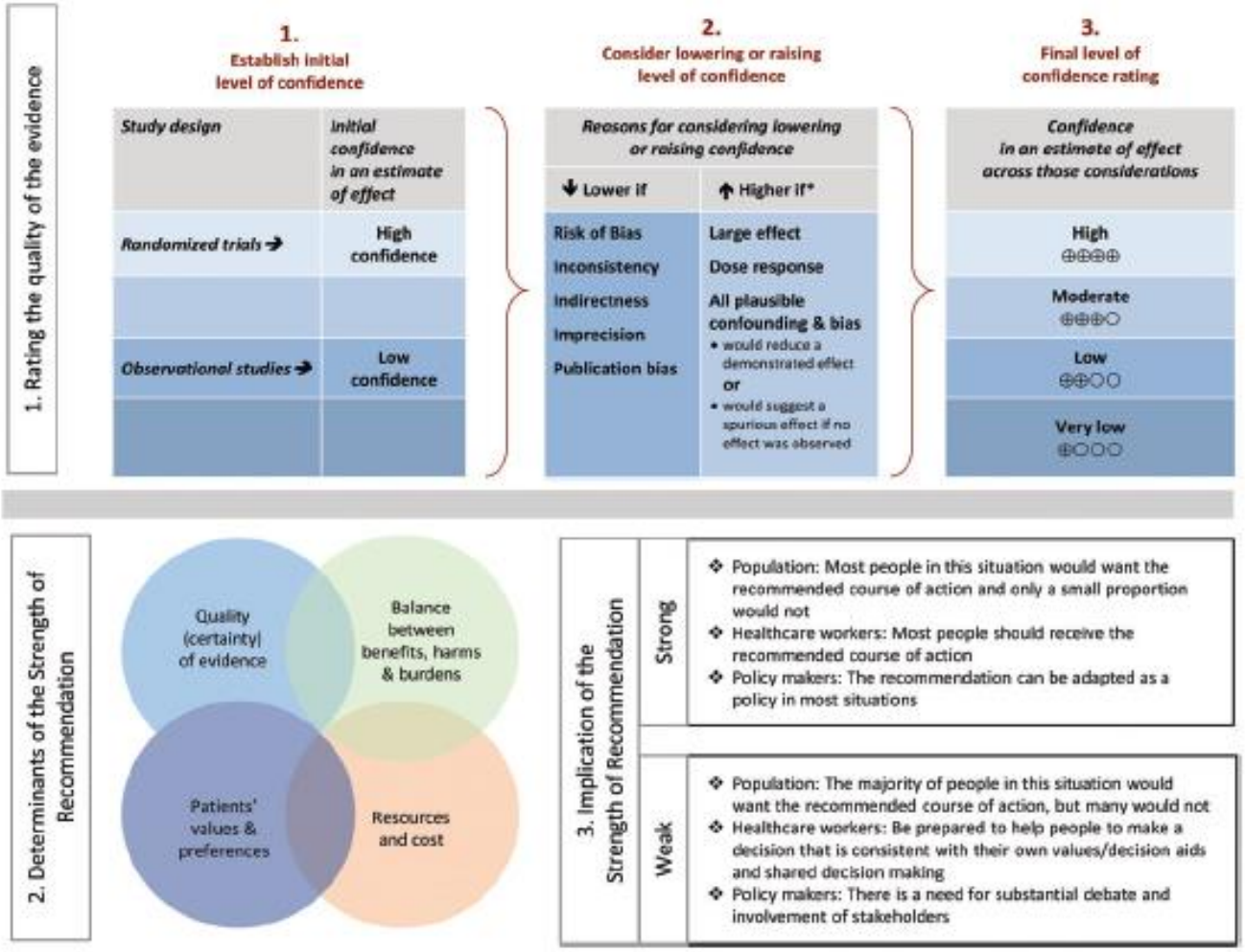

Table 14: Quality and Strength of evidence recommendation for non-GRADE methodologies (238)**.**

Strength of recommendation	A	Good evidence to support a recommendation for use.
	B	Moderate evidence to support a recommendation for use
	C	Poor evidence to support a recommendation
Quality of evidence	I	Evidence from 1 properly randomized, controlled trial. Experiments.
	II	Evidence from 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled.
	III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Table 15. Recommendations for the use of Echinocandins published in clinical practice guidelines.

Disease	Reference	Methodology	Quality of evidence and recommendation	Doses*	Comments
Candidemia in non-neutropenic Patients	(20)	GRADE (222) figure 1	strong recommendation; high-quality evidence	ANF: loading dose 200 mg, then 100 mg/day CSF: loading dose 70 mg, then 50 mg/day; MCF: 100 mg/day.	Recommended as initial therapy. AST should be performed if an echinocandin was used before
Candidemia in neutropenic Patients	(20)	GRADE (222) figure 1	strong recommendation; high-quality evidence	ANF: loading dose 200 mg, then 100 mg/day CSF: loading dose 70 mg, then 50 mg/day; MCF: 100 mg/day.	Recommended as initial therapy. AST should be performed if an echinocandin

					was used before
Chronic disseminated (hepatosplenic) candidiasis	(20)	GRADE (222) figure 1	strong recommendation; high-quality evidence	ANF: loading dose 200 mg, then 100 mg/day CSF: loading dose 70 mg, then 50 mg/day; MCF: 100 mg/day, for several weeks is recommended, followed by oral FLC, 400 mg (6 mg/Kg) daily	LAMB or an echinocandin can be used as initial therapy.
Empiric therapy for suspected candidiasis in non-neutropenic patients in the intensive care unit	(20)	GRADE	strong recommendation; high-quality evidence	ANF: loading dose 200 mg, then 100 mg/day CSF: loading dose 70 mg, then	An echinocandin is the preferred option

				50 mg/day; MCF: 100 mg/day.	
Prophylaxis to prevent invasive candidiasis in the intensive care unit setting	(20)	GRADE (222) figure 1	weak recommendation; low-quality evidence	ANF: loading dose 200 mg, then 100 mg/day CSF: loading dose 70 mg, then 50 mg/day; MCF: 100 mg/day.	Echinocandins are the alternative to the use of FLC 800-mg (12 mg/Kg) loading dose, then 400 mg (6 mg/Kg) daily
Candida intravascular infections, including Endocarditis and infections of Implantable Cardiac Devices	(20)	GRADE (222) figure 1	strong recommendation; high-quality evidence	ANF 300 mg/day, CSF 150 mg/day or MCF 150 mg/day.	High dose echinocandin is recommended as initial therapy together with LAMB alone or with 5FC

Treatment for *Candida* suppurative thrombophlebitis	(20)	GRADE (222) figure 1	strong recommendation; low-quality evidence	ANF 200 mg/day, CSF 150 mg/day, MCF 150 mg/day.	Catheter removal and drainage or resection of the vein, if feasible, is recommended firstly. LAMB or FLC can be used also.
Candida osteoarticular infections, osteomyelitis and septic arthritis	(20)	GRADE (222) figure 1	strong recommendation; low-quality evidence	ANF 100 mg/day, CSF 50-70 mg/day or MCF 100 mg/day.	FLC is suggested as the other possible treatment
Oropharyngeal candidiasis	(20)	GRADE (222) figure 1	weak recommendation; moderate-quality evidence	ANF 100 mg/day, CSF 50-70 mg/day or MCF 100 mg/day.	Treatment option for infections refractory to FLC

Invasive pulmonary aspergillosis, invasive sinus aspergillosis	(17)	GRADE(222) **figure 1**	weak recommendation; moderate-quality evidence	CSF (70 mg/day IV × 1, then 50 mg/day IV thereafter), MCF (100–150 mg/day IV),	Combined with VRC in selected patients. Alone if azoles and AMB are contraindicated. No mention of ANF in the guideline.
Empiric and pre-emptive Strategies in Allogeneic Stem Cell Transplant Recipients and patients treated for Acute Myelogenous Leukaemia	(210)	GRADE (222) **figure 1**	strong recommendation; high-quality evidence	MCF (50–100 mg/day), CSF (50 mg/day)	Only CSF and MCF are mentioned in the guideline.
Prevention of *Aspergillus* empyema (post aspergilloma surgical resection)	(210)	GRADE (222)**figure 1**	weak recommendation; low-quality evidence	CSF (70 mg/day IV × 1, then 50 mg/day IV thereafter), MCF (100–150 mg/day IV),	Should be used if the risk of surgical spillage of the aspergilloma

					is moderate to high
Salvage therapy of invasive aspergillosis	(18)	GRADE (24,239) figure 1	strong recommendation: moderate-quality evidence	CSF (70 mg/day IV × 1, then 50 mg/day IV thereafter), MCF (100–150 mg/day IV),	Echinocandins should be used alone or in combination.
Alternative as salvage therapy for *Aspergillus* infections when other azoles and LAMB cannot be used.	(18)	Canadian Task Force on the Periodic Health Examination (240,241) (**table14**)	BII	CSF (70 mg/day IV × 1, then 50 mg/day IV thereafter), MCF (100–150 mg/day IV),	Not recommended as primary treatment
Infection due to Azole resistant *Aspergillus* spp. (VRC MIC >2 mg/L)	(18)	Canadian Task Force on the Periodic Health Examination (238) (**table 14**)	CIII	CSF (70 mg/day IV × 1, then 50 mg/day IV thereafter), MCF (100–150 mg/day IV),	Echinocandin combined with VRC for individual patients

*Echinocandin drugs are mentioned in alphabetical order. ANF: anidulafungin, CSF: caspofungin, MCF: micafungin, FLC: fluconazole, 5FC: 5-fluorcytosine, LAMB: liposomal amphotericin B, VRC: voriconazole. AST: antifungal susceptibility testing. MIC: minimal inhibitory concentration. IV: intravenous.

11.2 Estimate of total patient exposure to date

Echinocandins were approved at the beginning of this century. Since then, they have been extensively used for prophylaxis and treatment of fungal infections including candidemia and deep-seated candidiasis, oesophageal candidiasis and some cases of invasive aspergillosis (azole-refractory and azole-intolerant). The exact number of patients treated with echinocandins is not known but we can estimate that millions have received an echinocandin treatment, given total market sales that exceeded $1 billion prior to generics coming onto the market.

11.3 Description of the adverse effects/reactions and estimates of their frequency

Echinocandins safety and tolerability profile is favourable and the adverse effects/reactions are mild to moderate. The mainly reported adverse effects are related to infusion reactions as phlebitis and fever, mild increases in liver enzymes, minor hypokalemia and unspecific signs as gastrointestinal discomfort, headache and skin rash (242–246).

Differences in frequencies of echinocandin-related adverse effects were observed when the three drugs were compared. Overall, anidulafungin seems to produce less adverse reactions than the other two drugs of the class. However, fewer safety studies were done for this echinocandin (245). When randomized trial data was evaluated, echinocandin treatment-related liver adverse effects (e.g. enzymes augment) are mild and less frequent than fluconazole and amphotericin B (comparator drugs) (71,220,247).

11.3.1 Anidulafungin

Adverse event rates were similar for anidulafungin and fluconazole when compared in trials (71). However, a lower incidence of liver-associated abnormalities was observed for this echinocandin. The most common adverse effects were diarrhoea, hypokalemia and elevated levels of ALT (all ≤3% of the patients).

11.3.2 Caspofungin

Caspofungin was better tolerated than amphotericin B. Nephrotoxicity and hypokalemia was observed in both groups but they were significantly less frequent and milder in the echinocandin treated group, and nephrotoxicity is possibly not related. Liver function markers abnormalities were also mild and observed in only 8% of the patients treated with caspofungin. The most important undesirable effects of this echinocandin were the infusion related ones (phlebitis, chills, rigors and fever), as the infusion solution is quite acidic. Nevertheless, a reduction in the rate of infusion or the infusion using a central venous catheter reduce these symptoms and avoid phlebitis (247).

11.3.3 Micafungin

As the other echinocandins, this drug´s most frequent related adverse effects are the infusion-related reactions, hypokalemia, abdominal discomfort and nausea and elevation of liver enzymes (220). In the trial where micafungin was compared with caspofungin, no differences in adverse events (liver function, nausea, hypokalemia and rash) were observed. However, adverse effects were not divided per treatment (248). As an exclusive aspect, hepatocellular tumours were observed in rat models using human therapeutic doses of micafungin. However, these effects were found after at a prolonged exposure (> 3 months) (249), and neither caspofungin nor anidulafungin were subjected to the same long term experiment. The European Medicines Agency imposed a 'black box' warning and extensive phase 4 pharmacovigilance requirements unlike the Food and Drug Administration (244,250). A case control US multicentre cohort study of hospitalized patients who received micafungin or other parenteral antifungals between 2005 and 2012 using propensity score matching and follow up hepatocellular carcinoma mortality identified through the National Death Index though to the end of December 2016. Of 40,110 patients treated with antifungals, 6,903 received micafungin and were successfully matched to 16,317 controls. Ten incident hepatocellular carcinoma deaths were identified, one in the micafungin-exposed group and nine among comparator antifungals over 71,285 person-years of follow-up, 0.05 per 1000 person-years in micafungin patients and 0.17 per 1000 person-years for

other antifungals. The propensity score-matched hazard ratio for micafungin versus comparator was 0.29 (95% CI 0.04-2.24) (251).

In a retrospective cohort study, which combined data from two large US- based hospital electronic medical record databases. Severe hepatotoxicity was defined as (Grade ≥ 3 liver function test) (LFT) after echinocandin initiation. Patient exposures included anidulafungin (n = 1,700), caspofungin (n = 4,431), or micafungin (n = 6,547). Differing proportions of patients had severe liver toxicity before echinocandin initiation: anidulafungin 40.4%; caspofungin 25.9% ($p < 0.001$); micafungin 25.6% ($p < 0.001$). Adjusted incidence rate ratios of severe hepatotoxicity for anidulafungin versus caspofungin and micafungin were 1.43 ($p = 0.002$) and 1.19 ($p = 0.183$) overall, and 0.88 ($P = 0.773$) and 0.97 ($P = 0.945$) for those with normal baseline LFTs, respectively. These data are indicative of very little difference between the drugs in hepatotoxicity (252).

Table 16: Frequency of adverse effects with echinocandin treatments.

Adverse effect	Anidulafungin [a]	Caspofungin [b]	Micafungin [c]
Abdominal pain	<2	3.6	1
Diarrhoea	3.1	3.6	1.6
Fever	< 1	4-40	1-14
Headache	1.3	4-15	2-17
Hypokalemia	3-10	2-10	1.2
Leukopenia	< 1	6.2	1.6

Liver function test abnormalities	3-5	1-15	1-8
Nausea / vomiting	1 / < 1	1-6 / 2-4	2-7 / 1-5
Neutropenia	1	1.9	1.2
Phlebitis	< 1	3.5-25	1.6
Rash / pruritus	1 / <2	1-10 / < 2	1-12 / <1
Thrombocytopenia	< 2	3.1	< 1

[a] % of patients. Obtained from (209,253).
[b] % of patients. Obtained from (143,145,201,207,254).
[c] % of patients. Obtained from references: (208,228,255–257)

11.4 Drug-Drug Interactions

Interactions were described already in the section 7.3. There are few drug interactions with echinocandins. Echinocandins are poor substrates for cytochrome P450 enzymes. Thus, co-administration with CYP inhibitors or inductors (e.g. carbamazepine, phenytoin, etc.) are clinically insignificant.

Caspofungin may interact with halogenated penicillins (e.g. dicloxacillin) as the potentially induce CYP3A4 enzyme (258–261).Clinically significant interactions with caspofungin were documented with rifampicin, tacrolimus and ciclosporin (27,213,262). This last drug showed clinically significant interactions with micafungin but this effect was inexistent when co-administered with anidulafungin (24,239).

11.4.1 Identification of variation in safety that may relate to health systems and patient factors

There are no known ethnicity or gender specific toxicities.

12 Summary of available data on comparative cost and cost-effectiveness of the medicine.

Several pharmacoeconomic evaluations were published comparing echinocandins with azoles (fluconazole and voriconazole), echinocandins with amphotericin B and two or the three echinocandins between each other (a summary of them are in table 19). Amphotericin B cost was evaluated in its deoxycholate form (even it is not recommended due to its high toxicity) mostly in low-income countries while lipid formulations of amphotericin B were compared with echinocandins in middle to high-income countries. The costs were estimated mostly as the addition of the drug acquisition cost, treatment cost itself (oral for fluconazole vs IV treatment for echinocandins), cost of medical attention (health personal honoraria, ICU stay cost, etc.), and the associated cost of the treatment of impaired renal function (by amphotericin B). Few reports included into their cost estimations the so-called concept of life-years gained (modified mortality measure where remaining life expectancy is considered). This method accrues more importance to saving the life of a young person (> life years than an elderly).

Few reports compared one echinocandin vs. other drug of the same group and in some of them, caspofungin was cheaper and in other micafungin was the more cost-effective option (**table 20**). When lipid-amphotericin B and fluconazole were compared with any of the echinocandins, the last class of antifungals were regarded as cost effective especially in high-income countries since the health personal cost and other associated cost are higher than in low-income countries. In low- and middle-income countries the potentially toxic deoxycholate amphotericin B and the less effective fluconazole (high secondary resistance rates) are regarded as more cost-effective the echinocandins. In these countries, the major cost drivers are the drug acquisition costs. For this reason, we consider that if echinocandins are included in the WHO EML list, the cost of acquiring these drugs will decrease in these countries, making them economically competitive. This will result in a better care for critically ill patients who receive this type of drugs, reducing the differences in the quality of care between countries.

Table 17: Pharmacoeconomic studies for echinocandins.

Year	Compared ATF	Result (Cost)	Infection	Major cost driver/conclusion	Country	Reference
2005	CSF vs LAMB	CSF < LAMB	candidemia	Drug acquisition cost and treatment of impaired renal function (caused by AMB)	USA	(263)
2008	CSF vs LAMB and AMB	AMB lowest cost high toxicity	IA	Drug acquisition costs and other expenditures. AMB remains the option of choice for its cost	Turkey	(264)
2007	CSF vs LAMB	CSF < LAMB	Empirical treatment of febrile neutropenia	Drug acquisition cost and treatment of impaired renal function (caused by AMB)	USA	(265)

2009	CSF vs VRC, LAMB, AMB and ITC	VRC is the most cost effective	IA	Not described	Review (6 different countries)	(266)
2009	CSF vs MCF	MCF<CSF (not significant)	IC	MCF lower price and better results	UK	(267)
2009	MCF 150 mg vs 100 mg	100 mg similar outcome than 150 mg	candidemia	Use 100 mg/day	USA	(268)
2010	ECD vs FLC and LAMB	FLC<ECD<LAMB		ECD limited to azole R and IA salvage therapy	India	(269)
2011	ECD vs non-ECD	echinocandins may be cost-effective		Hospitalization	USA	(270)
2011	ANF vs FLC	ANF>FLC however is cost-effective in an Australian perspective	IC	ANF cost > AU$25000 per life-years gained	Australia	(271)
2011	ANF vs FLC	ANF better clinical outcomes < cost (< ICU and hospitalization stay)	Candidemia and IC	clinical outcomes, resource use and cost measures	USA	(159)

2011	ECD vs Non-ECD	Similar cost than other therapies		MCF is cost-effective for prophylaxis in high FLC-R settings	Review (different countries)	(241)
2012	CSF vs VRC	CSF cost < VRC (no statistically significant)	Empirical treatment of febrile neutropenia	Not described	Australia	(272)
2013	MCF vs LAMB	MCF < LAMB	Candidemia	Hospitalization (length of stay was shorter with MCF)	Australia	(273)
2013	CSF vs MCF	MCF<CSF	Candidemia and IC	Drug acquisition	Australia	(274)
2013	CSF vs LAMB	CSF cost < LAMB	Empirical treatment IFI	Not described	Turkey	(275)
2013	CSF vs VRC, LAMB and PSC	CSF cost < LAMB but PSC is better	Antifungal prophylaxis of IFI and IA	Hospitalization	Canada	(276)
2014	CSF vs VRC	CSF cost < VRC	Empiric therapy in febrile neutropenia	treatment duration and acquisition cost	Turkey	(277)
2016	ANF+VRC vs VRC	Combination is cost-effective in HD and	IA	Drug cost and adverse event rates	Spain	(278)

		HSCT patients with positive galactomannan				
2017	ECD Vs LAMB and FLC	ECD are cost-effective and economical		Not described	USA	(279)
2017	ANF Vs FLC	ANF is cost effective	IC	Drug acquisition cost (ANF) and hospitalization (FLC)	Turkey	(280)
2017	CSF and MCF vs FLC	FLC < ECD	Prevent fungal infections	Not described	China	(281)
2017	ECD vs FLC	ECD < FLC (specially ANF)	IC	Life-year gained	Taiwan	(282)
2018	CSF vs MCF	CSF < MCF	Candidemia and IC	Drug acquisition	Turkey	(283)

ANF: anidulafungin, CSF: Caspofungin, MCF: Micafungin, LAMB: liposomal amphotericin B, AMB: amphotericin B deoxycholate, ITC: itraconazole. ATF: antifungal, ECD: echinocandins, FLC: fluconazole, VRC: voriconazole, PSC: posaconazole

IC: invasive candidiasis, IA: Invasive Aspergillosis, ND: No data, HD: hematologic disease, HSCT: haematopoietic stem cell transplant, IFI: invasive fungal infections.

13 Summary of regulatory status and market availability of the medicine.

13.1 US Food and Drug Administration

13.1.1 Anidulafungin indicated in adults for the treatment of:

- Candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis)
- Oesophageal candidiasis
- Limitations of use: has not been studied in endocarditis, osteomyelitis and meningitis due to *Candida* or in sufficient numbers of neutropenic patients

13.1.2 Caspofungin acetate for injection is indicated in adults and paediatric patients (3 months of age and older) for:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections.
- Treatment of oesophageal candidiasis.
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

13.1.3 Micafungin is indicated for:

- Treatment of patients with candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses.
- Treatment of patients with oesophageal candidiasis.
- Prophylaxis of *Candida* Infections in patients undergoing haematopoietic stem cell transplantation.

13.2 European Medicines Agency

13.2.1 Anidulafungin for infusion was approved for:

- Treatment of invasive candidiasis in adult patients

13.2.2 Caspofungin acetate for infusion was approved for:

- Empirical therapy of presumed fungal infections in febrile, neutropenic adult patients.
- Salvage therapy in treatment of invasive aspergillosis in adult patients whose disease is refractory to, or who are intolerant of, other antifungal agents (i.e., conventional or lipid formulations of amphotericin B and/or itraconazole).
- Invasive candidiasis in adult patients.

13.2.3 Micafungin for infusion was approved for:

- Adults, adolescents ≥ 16 years of age and elderly:
    - Treatment of invasive candidiasis.
    - Treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate.
    - Prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells / µl) for 10 or more days.
- Children (including neonates) and adolescents < 16 years of age:
    - Treatment of invasive candidiasis.
    - Prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells / µl) for 10 or more days.

13.3 Japanese Medicines Agency

(The Pharmaceuticals and Medical Devices Agency)

13.3.1 Anidulafungin is not approved in Japan:

13.3.2 Caspofungin was approved for:

- Treatment of deep-seated *Candida* or *Aspergillus* infections in febrile, neutropenic adult patients.

13.3.3 Micafungin was approved for adults and for paediatric patients for:

- Treatment of fungaemia
- Treatment of respiratory mycosis
- Treatment of gastrointestinal mycosis

13.4 Generic availability and international brand names

Caspofungin was the first approved drug of the echinocandin class of antifungals. It was approved by FDA on January 26th, 2001 as caspofungin acetate intravenous powder. It was firstly manufactured by MERCK and its US brand name is Cancidas (43,284). Later, on June 15th, 2005, the second echinocandin was approved by FDA as mycafungin sodium for injection. Its approval was sponsored by Fujisawa Healthcare, INC. and its US brand name is Mycamine (46,285). In February 17th, 2006, the last member of this class was FDA-approved as anidulafungin for injection. Its approval was requested by Vicuron, a subsidiary of Pfizer inc. and its US brand name is Eraxis (41,286).

Since those approvals several different brand names were used in different countries and for caspofungin, there are different approved generic versions that are considered as equivalent (**Figures 2 to 4. Tables 18 to 20**). The maps were generated from listing by the companies of registrations and from GAFFI Ambassadors in each country. https://www.gaffi.org/antifungal-drug-maps/.

Figure 2. Anidulafungin country registrations

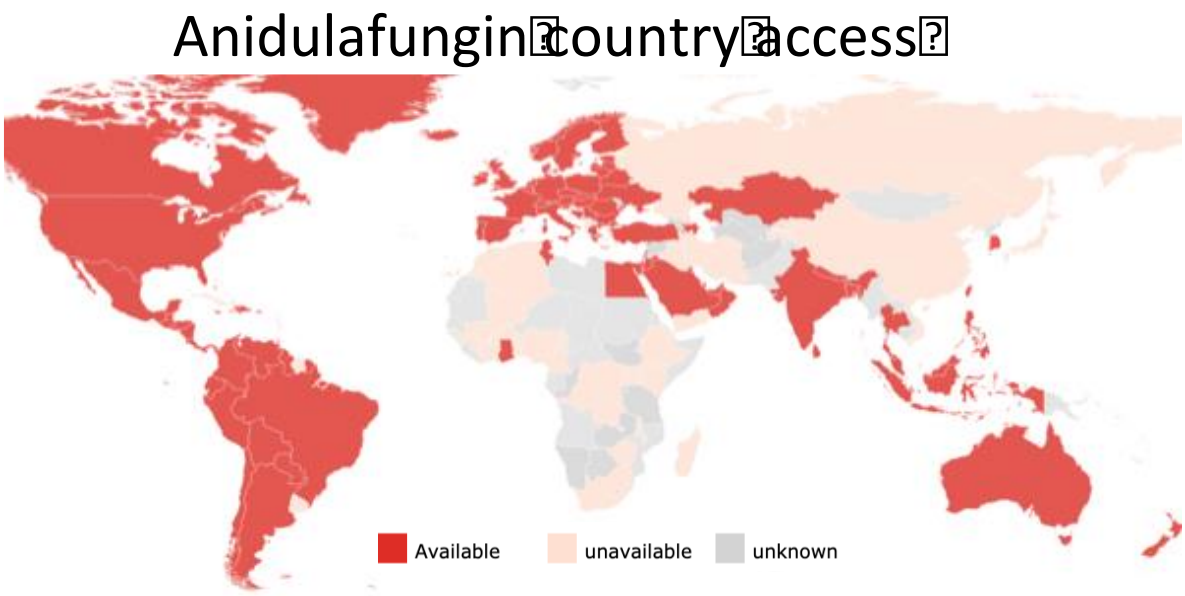

Figure 3. Country registrations of caspofungin

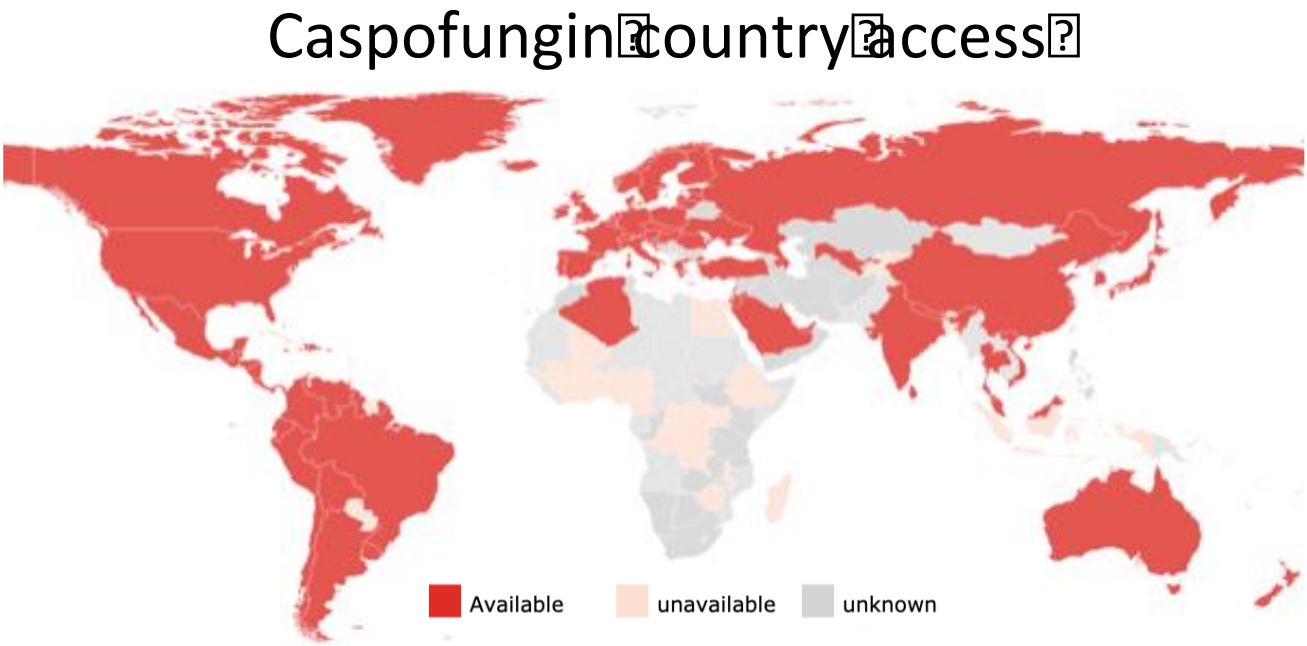

Figure 4. Country registrations of micafungin

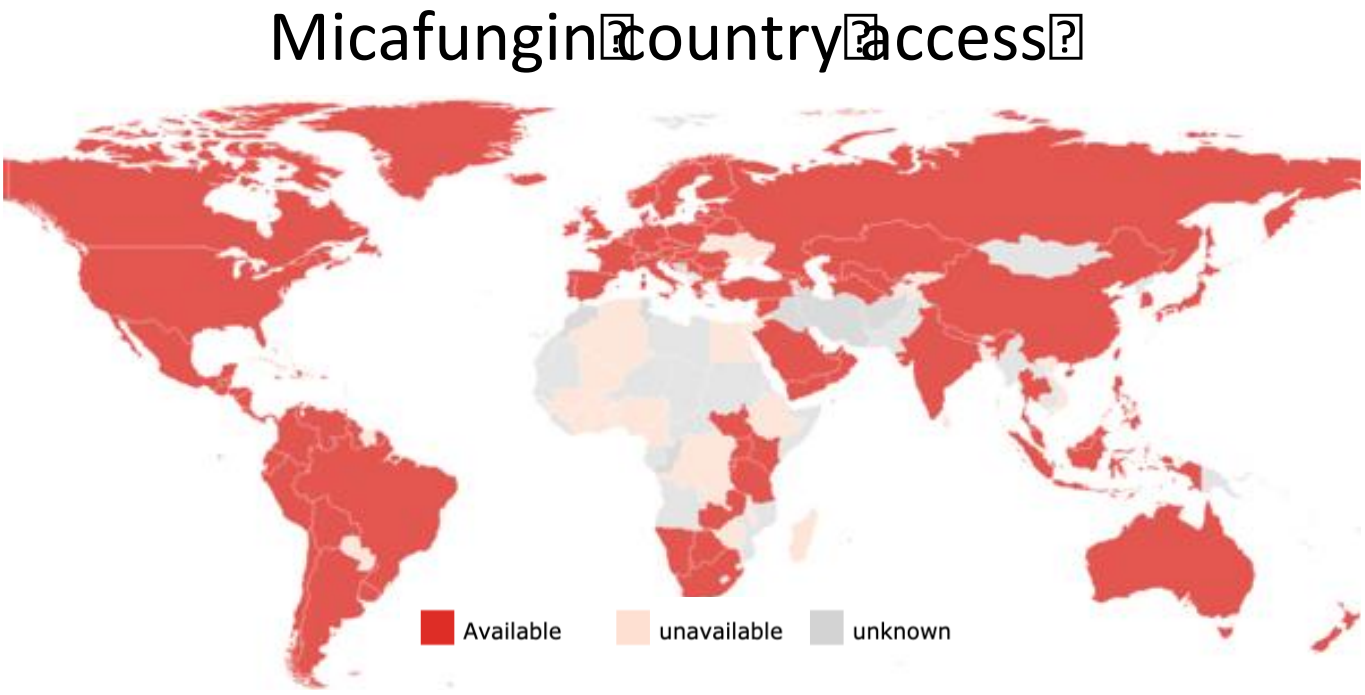

Table 18: Eraxis/Ecalta (Anidulafungin) brand names and manufacturer in different countries (286).

Brand Name	Manufacturer	Country
Ecalta	Haemato Pharm	Austria
Eraxis	Pfizer	Australia, Canada, Hong Kong, Malaysia, Philippines, Thailand, Turkey, Taiwan, United States
Ecalta	Pfizer	Austria, Hungary, Luxembourg, Oman, Switzerland, Latvia, Chile, Argentina, Belgium, Brazil, Colombia, Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Croatia (Hrvatska), Indonesia, Ireland, Lithuania, Norway, Peru, Poland, Portugal, Sweden, Slovakia, Tunisia, Serbia, Italy, Iceland, Netherlands, Romania
Eraxis	Pharmacia	Israel
Orrakrutt	Sigillata	Netherlands
Anidulafungin Sigillata	Sigillata	United Kingdom
Anidulafungin Teva	Teva	Portugal and United Kingdom
Fuxesin	Vem Ilac	Turkey
Anidulafungina Wyeth Pharma	Wyeth Pharma	Brazil

Table 19: Brand names in different countries and generic Cancidas (caspofungin acetate) marketed (284).

Brand Name/generic	Generic Manufacturer (In alphabetic order)	Country
Cancidas (original brand name under patent)	Merck	Iceland, United States, Canada
	Merck Sharp & Dohme	Australia, Austria, Brazil, Bosnia & Herzegovina, Chile, China Croatia (Hrvatska), Cyprus, Ecuador, Estonia, Greece, Hong Kong, Lithuania, Macedonia, Malaysia, Netherlands, New Zealand Italy, Philippines, Romania, Serbia, Singapore, Spain, Taiwan, United Kingdom, Venezuela
	MSD	Argentina, Belgium, Costa Rica, Czech Republic, Denmark, El Salvador, Finland, France, Germany, Guatemala, Honduras, Hungary, Ireland, Israel, Japan, Lebanon, Luxembourg, Nicaragua, Norway, Panama, Peru, Poland, Serbia, Slovakia, South Africa, Sweden, Switzerland, Thailand, Turkey, Vietnam.
	Cibeles	Uruguay
Caspofungin 1A Pharma	1A Pharma	Malta
Caspofungin Accord	Accord Healthcare	Estonia, Greece, Lithuania, Poland, Romania, Sweden
Kaspofungin Accord	Accord Healthcare	Slovenia
Caspofungin Actavis	Actavis	Sweden

Caspofungin Adamed	Adamed	Poland
Caspofungine Altan	Altan Pharma	Netherlands
Dalvocans	Alvogen	Estonia, Lithuania, Malta, Poland, Romania
BDCASPO	Ambica	Philippines
Caspofungin Amneal	Amneal	Malta
Caspofungin Antibiotice	Antibiotice	Malta
Caspofungina ATB	Antibiotice	Romania
Caspofungin Mylan	Arcana Arzneimittel	Austria
Caspofungin B. Braun	B. Braun	Malta
Caspofungin-Humanity	BDR Pharmaceuticals	Georgia
Caspofungin Cadiasun	Cadiasun	Netherlands
Caspofungine CF	Centrafarm	Netherlands
Caspofungin	Consilient Health	United Kingdom
Caspofungin Demo	Demo	Greece
Caspofungin	Dr. Reddy´s	United Kingdom
Kafum	Dr. Reddy´s	Colombia
Caspofungin DSM Sionchem Pharmaceuticals	DSM Sionchem Pharmaceuticals	Malta
Caspofungin Fresenius Kabi	FRESENIUS KABI USA	Poland, US (approval date Dec. 30 2016)

Caspofungin Galenicum	Galenicum	Malta
Caspovitae	Galenicum	Peru
Caspofungin	Generics UK	United Kingdom
Caspofungina Genfarma	Genfarma	Poland and Spain
Caspofungin Gland Pharma	GLAND PHARMA LTD	US (approval date Sept 29 2017)
Casfung	Glenmark	India
Casokan	Heaton	Malta and Romania
Caspofungin Hikma	Hikma	Malta
Caspofungine Hikma	Hikma Pharma Benelux	Netherlands
Caspofungin Ibigen	Ibigen	Malta
Caspofungin Inresa	Inresa	Germany
Caspofungin Jiangsy Hengrui	JIANGSU HENGRUI MED	US (approval date Jun 28 2018)
Fungidas	Kocak Farma	Turkey
Caspofungin Macarthys	Macarthys	Malta
Caspofungin MYX	Mayne Pharma	Australia
Caspofungin MDA	MDA	Canada
Afundas	Mustafa Nevzat	Turkey

Caspofungin Mylan	Mylan Labs LTD	Malta, Netherlands, Poland, Romania, Sweden, US (approval date Sept 29 2017)
Caspofungin Orion	Orion Pharma	Sweden
Casfucid	Pharmaceutical	Peru
Dalvocans	Pharmadox	Bulgaria
Kaspofungin PharmaS	PharmaS	Croatia (Hrvatska)
Casmyg	Pharmathen	Greece
Dalvocans	Pharmathen	Bulgaria
Caspofungin-Pharmore	Pharmore	Germany
Kaspofungin Piva	Piva	Croatia (Hrvatska)
Caspofungin Ranbaxy	Ranbaxy	Poland, United Kingdom
Caspofungina Ratiopharm	Ratiopharm	Germany and Romania
Caspofungin ratiopharm	Ratiopharm Arzneimittel	Austria
Caspofungine Regiomedica	Regiomedica	Netherlands
Kaspofungin Regiomedica	Regiomedica	Sweden
Caspofungin Sandoz	Sandoz	Estonia, Lithuania, Poland, Sweden
Caspofunine Sandoz	Sandoz	Netherlands
Kaspofungin Sandoz	Sandoz	Croatia (Hrvatska)
Caspofungin Solinea	Sollinea	Poland

Caspofunign Stada	Stada	Poland, Romania, Sweden
Caspofunign Stada	Stada Arzneimittel	Austria
Caspofungin Teva	Teva	Belgium, Czech Republic, Estonia, Lithuania, Malta, Poland, Slovakia, Sweden, Romania
Caspofungina Teva	Teva	Spain
Caspofungine Teva	Teve Nederland	Netherlads
Cancas	Ven Ilac	Turkey
Fungizor	Vocate	Greece
Caspofungin Xelia	XELLIA PHARMS APS	Bulgaria, Estonia, Lithuania, Poland, Sweden, US (approval date Jul 2, 2018)
Caspofungina Zentevia	Zentevia	Romania
Caspofungin Zentiva	Zentiva	Poland, United Kingdom

Table 20: Mycamine (Mycafungin) brand names in different countries and manufacturers (285)

Brand Name	Manufacturer (In alphabetic order)	Country
Mycamine	Astellas	Austria, Australia, Brazil, Canada, China, Croatia (Hrvatska), Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Hong Kong, Hungary, Iceland, Indonesia, Ireland, Israel, Italy, Latvia, Lithuania, Netherlands, Norway, Philippines, Poland, Romania, Serbia, Singapore, Slovakia, Slovenia, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, United States.
	Hikma	Lebanon
	Astellas Pharma Europe BV	Greece
	DKSH	Malaysia
	Fujisawa	United States
	Raffo	Argentina
Funguard	Astellas	Japan

14 Availability of pharmacopeial standards

(British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

The three echinocandins were searched in the following pharmacopoeias:

• The British Pharmacopoeia

• The International Pharmacopoeia

• The United States Pharmacopoeia

• The European Pharmacopoeia

No echinocandin is available in any of the named pharmacopoeia standards neither in:

- https://online.epocrates.com
- https://www.drugs.com/search.php?searchterm=anidulafungin
- https://www.drugs.com/search.php?searchterm=caspofungin
- https://www.drugs.com/search.php?searchterm=micafungin

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