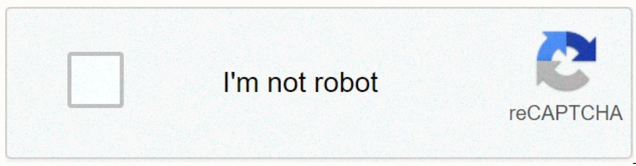

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Candidiasis in pregnancy guidelines

Published in CID, 12/16/2015 Clinical Infectious Diseases, Volume 62, Issue 4, 15 February 2016, Pages e1-e50, 16 December 2015 Peter G. Pappas, Carol A. Kauffman, David R. Andes, Cornelius J. Clancy, Kieren A. Marr, Luis Ostrosky-Zeichner, Annette C. Reboli, Mindy G. Schuster, Jose A. Vazquez, Thomas J. Walsh, Theoklis E. Zaoutis, Jack D. Sobel The full document, including tables and references, please visit the Oxford University Press website. It is important to recognize that the guidelines do not always account for individual differences in patients. They are not intended to displace the doctor's judgment regarding certain patients or specific clinical situations. THE IDSA considers that compliance with these guidelines is voluntary and should apply the final definition of their use by the doctor in the light of the individual circumstances of each patient. Keywords: candidemia, invasive candidiasis, fungal diagnostics, azoles, echinocandins Background Invasive infection due to Candida species is largely a condition that is medically developing and is widely recognized as the main cause of morbidity and mortality in the health environment. There are at least 15 different Candida species that cause human disease, but >90% of the invasive disease is caused by 5 of the most common pathogens, C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei. Each of these organisms has unique virulence potential, antifungal sensitivity and epidemiology, but overall, significant infections caused to such organisms are usually called invasive candidiasis. Mucosal Candida infections, especially those affecting oropharynx, esophagus, and vagina are not considered classically invasive diseases, but they are included in these guidelines. Since the last iteration of these guidelines in 2009 [1], new data have been available on the diagnosis, prevention and treatment of proven or suspected invasive candidiasis, leading to significant changes to our treatment recommendations. The revised recommendations for the treatment of candidiasis in 2016 are summarised below. Given the relevance of the guidance to pediatrics, the guidelines have been reviewed and approved by the American Academy of Pediatrics (AAP) and the Society for Pediatric Infectious Diseases (PIDS). The Mycoses Study Group (MSG) has also approved these guidelines. The board followed a guidance development process adopted by the American Society for Infectious Diseases (IDSA), which systematically classizes both the quality of evidence (very low, low, moderate and high) and the strength of the recommendation (weak or strong) [2] (Figure 1). [3] The guidelines are not intended to replace clinical judgement in the treatment of individual patients. A detailed description of the methods, background and evidence supporting each proposal can be found in the full text. guidelines. I. What is the treatment for Candidemia in nonneutropenic patients? Echinocandin (caspofungin: load dose 70 mg, then 50 mg per day; micafungin: 100 mg per day; anidulafungin: load dose 200 mg, then 100 mg per day) is recommended as an initial therapy (strong recommendation; high-quality evidence). Fluconazole, intravenous or oral, 800 mg (12 mg/ kg) load dose, followed by 400 mg (6 mg/ kg) per day is an acceptable alternative to echinocandin as an initial therapy for selected patients, including those who are not in critical condition and who are not considered likely to be a fluconazol-resistant Candida species (strong recommendation; high-quality evidence). A study of azol sensitivity is recommended in all bloodstreams and other clinically significant Candida isolates. Consideration should be given to examining echinocandin sensitivity in patients who have previously been treated with echinocandin and among those with C. glabrata or C. parapsilosis (strong recommendation; low-quality evidence). The transition from echinocandin to fluconazole (usually within 5-7 days) is recommended for patients who are clinically stable, have fluconazol-sensitive isolates (e.g. albicans.C and negative repeated blood cultures after initiation of antifungal treatment (strong recommendation; moderate quality evidence). In the case of infection with C. glabrata, the transition to higher doses of fluconazole (12 mg/kg) daily or voriconazole 200-300 (3-4 mg/kg) twice a day should only be considered in patients with fluconazole sensitivity or voriconazole-sensitive isolate (strong recommendation; low-quality evidence). Lipid preparation amphotericin B (AmB) (3-5 mg/kg per day) is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents (strong recommendation; high quality evidence). The transition from AmB to fluconazole is recommended after 5-7 days in patients whose fluconazol-sensitive isolates are clinically stable and for whom cultures repeated in antifungal therapy are negative (strong recommendation; high-quality evidence). AmB lipid preparation (3-5 mg/kg per day) (strong recommendation; low-quality evidence) is recommended in patients with suspected azol and echinocandin-resistant Candida infection. Voriconazole 400 mg (6 mg/kg) twice a day in 2 doses, followed by 200 mg (3 mg/ kg) twice a day is effective for candidemia, but offers few benefits over fluconazole as an initial therapy (strong recommendation; moderate-grade evidence). Voriconazole is recommended as step-down oral therapy in selected cases of candidemia due to C. krusei (strong recommendation; low-quality evidence). All non-neutropenia patients with candidemia should conduct dilated ophthalmic examinations within the first week of diagnosis, preferably by ophthalmologist (strong recommendation; low-quality evidence). Blood formation should be carried out every day every other day to determine the date when candidiaemia was clarified (strong recommendation; low quality evidence). Recommended duration of therapy for candidemia without obvious post-2 weeks of documented clearance of Candida species into the bloodstream, and resolution of symptoms attributed to candidemia (strong recommendation; moderate-quality evidence). II. Should the middle vein catheters be removed from nonneutropenic patients with candidemia? Central venous catheters (CVCs) during candidemia should be removed as soon as possible if the source is classified as CVC and the catheter can be safely removed; this decision should be taken individually for each patient (strong recommendation; moderate quality evidence). III. What is the treatment of Candidemia in neutropenic patients? Echinocandin (caspofungin: load dose 70 mg, then 50 mg daily; micafungin: 100 mg per day; anidulafungin: load dose 200 mg, then 100 mg per day) is recommended as an initial therapy (strong recommendation; moderate quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, is an effective but less attractive alternative because of its potential toxicity (strong recommendation; moderate quality evidence). Fluconazole, the load dose of 800 mg (12 mg/kg), followed by 400 mg (6 mg/kg) per day, is an alternative to patients not in critical condition and has not previously had exposure to azol (poor recommendation; low-quality evidence). Fluconazole, 400 mg (6 mg/kg) per day, can be used for step-down therapy during persistent neutropenia in patients with clinically stable, sensitive isolates and documented bloodstream clearance treatment (poor recommendation; low-quality evidence). Voriconazole, 400 mg (6 mg/kg) twice a day in 2 doses, followed by 200-300 mg (3-4 mg/ kg) twice a day, can be used in situations where additional mold coverage is desirable (poor recommendation; poor quality evidence). Voriconazol can also be used during neutropenia in clinically stable patients who have documented clearance of the bloodstream and isolates sensitive to voriconazole (poor recommendation; low-quality evidence). Infections caused by c. krusei, echinocandin, lipid preparation AmB, or voriconazol are recommended (strong recommendation; low quality evidence). Recommended minimum duration of therapy for candidiaemia without any 2 weeks of documented clearance candida from the bloodstream, provided neutropenia and symptoms attributed to candidemia are resolved (strong recommendation; low-quality evidence). Ophthalmic records of choroidal and vitreal infection are minimal until recovery from neutropenia; therefore, in the first week after recovery from neutropenia (strong recommendation; low-quality evidence), dilated funduscopical studies should be performed. In a neutropenic patient, sources of candidiasis differ from CVC (eg, gastrointestinal tract) dominate. Catheter (strong recommendation; low-quality evidence). Granulocyte colony-stimulating factor (G-CSF)-mobilized granulocyte transfusions can be considered in the case of persistent candidemia expected with prolonged neutropenia (poor recommendation; low-quality evidence). IV. What is the treatment of chronic disseminated (hepatosplenic) candidiasis? Initial therapy with lipid preparation AmB, 3-5 mg/kg per day or echinocandin (micafungin: 100 mg per day; caspofungin: 70 mg loading dose, then 50 mg daily; or anidulafungin: 200 mg loading dose, then 100 mg daily), recommended for several weeks, followed by oral fluconazole, 400 mg (6 mg/ kg) per day, in patients unlikely to have fluconazole-resistant isolate (strong recommendation; low-quality evidence). Therapy should be continued until the lesions are dissolved during repeated imaging, which is usually several months. Premature discontinuation of antifungal treatment can lead to relapse (strong recommendation; low-quality evidence). If chemotherapy or haematopoietic cell transplantation is required, it should not be delayed due to the presence of chronic disseminated candidiasis and antifungal therapy should be continued throughout the period of high risk for the prevention of relapse (strong recommendation; low-quality evidence). In patients who have desensitating persistent fever, short-term (1-2 weeks) treatment with nonsteroidal anti-inflammatory drugs or corticosteroids may be considered (poor recommendation; low-quality evidence). A. What is the role of empirical treatment in suspected invasive candidiasis nonneutropenic patients in the intensive care unit? Empirical antifungal therapy should be considered in critically ill patients who are not known to have risk factors for invasive candidiasis and other known causes of fever and should be based on a clinical assessment of risk factors, replacement markers for invasive candidiasis and/or culture from non-sterile sites (strong recommendation; moderate-quality evidence). Empirical antifungal therapy should be started as soon as possible in patients with the above risk factors and who have clinical signs of septic shock (strong recommendation; moderate quality evidence). Preferred empirical therapy for suspected candidiasis nonneutropenic patients in the intensive care unit (ICU) is an echinocandin (caspofungin: load dose 70 mg, then 50 mg per day; micafungin: 100 mg per day; anidulafungin: loading dose 200 mg, then 100 mg daily) (strong recommendation; moderate quality evidence). Fluconazole, a load dose of 800 mg (12 mg/kg), followed by 400 mg (6 mg/kg) per day is an acceptable alternative for patients who have not had fresh azol exposure and have not been colonised with azol-resistant Candida species (strong recommendation; moderate-quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, is an alternative if there is intolerance to other antifungal agents (strong recommendation; low-quality evidence). Recommended duration of empirical therapy suspected invasive candidiasis in patients who improve by 2 weeks is the same as treatment documented candidemia (poor recommendation; low quality evidence). Patients who do not have a clinical response to empirical antifungal treatment at 4-5 days of age and who have no subsequent evidence of invasive candidiasis after initiation of empirical therapy or who have a negative non-culture-based diagnostic study with a high negative predictive value should consider discontinuing antifungal therapy (strong recommendation; low-quality evidence). VI. Should prophylaxis be used to prevent invasive candidiasis in the intensive care unit setting? Fluconazole, a load dose of 800 mg (12 mg/kg), followed by 400 mg (6 mg/kg) per day, can be used in high-risk, high-proportion adult IJs with a high (>) ratio. (poor recommendation; moderate-quality evidence). Another option is to take an echinocandin (caspofungin: 70 mg loading dose, then 50 mg daily; anidulafungin: 200 mg load dose, then 100 mg daily; or micafungin: 100 mg per day) (poor recommendation; poor quality evidence). Daily bathing in patients in the intensive care unit with chlorhexidine may be considered, which has been shown to reduce the incidence of infections in the bloodstream, including candidemia (poor recommendation; moderate-quality evidence). VII. What is the treatment of neonatal candidiasis, including central nervous system infection? What is the treatment of invasive candidiasis and candidiaemia? AmB deoxycolate, 1 mg/kg per day, is recommended for neonate-distributed candidiasis (strong recommendation; moderate-grade evidence). Fluconazole, 12 mg/kg intravenous or daily oral, is a reasonable alternative in patients who have not received fluconazole prophylaxis (strong recommendation; moderate quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, is an alternative, but should be used with caution, especially in the presence of urinary tract affected (poor recommendation; low-quality evidence). Echinocandins should be used with caution and should generally be limited to rescue therapy or situations where resistance or toxicity precludes the use of AmB deoxyzole or fluconazole (poor recommendation; low-quality evidence). Lumbar pustion and dilated retinal examination are recommended in neons that have positive cultures (strong recommendation; low-quality evidence) for Candida species from blood and/or urine. Computed tomography or ultrasonic imaging of the urogenital tract, liver and spleen should be carried out if the blood cultures are persistently positive for Candida species (strong recommendation; low-quality evidence). Removal of CVC is highly recommended (strong recommendation; moderate quality evidence). The recommended duration of treatment of candidiaemia without obvious lytic complications is 2 weeks after documented excretion of Candida species from the bloodstream and resolution of symptoms attributable to candidemia (strong recommendation; weak What is the treatment for CNS infections neonates? For initial treatment, AmB deoxycolate, 1 mg/kg intravenous daily, is recommended (strong recommendation; low quality evidence). An alternative treatment is liposomal AmB, 5 mg/kg per day (strong recommendation; low quality evidence). This addition of flucytosin, 25 mg/kg 4 times a day, is considered residual therapy in patients who have not responded clinically to initial AmB treatment, but side effects are common (poor recommendation; low-quality evidence). After the discharge treatment, the patient responded to initial treatment, fluconazole, 12 mg/kg per day, recommended isolates that are sensitive to fluconazole (strong recommendation; low-quality evidence). Therapy should continue until all signs, symptoms and cerebrospinal fluid (CSF) and radiological disorders, if present, are eliminated (strong recommendation; low-quality evidence). Infected central nervous system (CNS) devices, including ventriculostomy channels and stents, should be removed, if at all possible (strong recommendation; low-quality evidence). What are the recommendations for prophylaxis in the neonatal intensive care unit setup? The high proportion of nurseries (>10%) invasive candidiasis, intravenous or oral fluconazole prophylaxis, 3-6 mg/kg twice a week for 6 weeks, newborns with birth weight <1000 g recommended (strong recommendation; high quality evidence). Oral nystatin, 100,000 units per day 3 times for 6 weeks, is an alternative to fluconazole with neonazole birth weight <1500 g in situations where availability or resistance excludes fluconazole (poor recommendation; moderate quality evidence). Oral bovine lactoferrin (100 mg per day) may be effective for neonate < 1500 g, but is not currently available in U.S. hospitals (poor recommendation; moderate quality evidence). VIII. What is the treatment of intra-abdominal candidiasis? Empirical antifungal therapy should be considered in patients with clinical evidence of abdominal infection and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leakage or necrotizing pancreatitis (strong recommendation; moderate quality evidence). Treatment of abdominal candidiasis should include source control with adequate drainage and/or cleaning (strong recommendation; moderate quality evidence). The choice of antifungal therapy is the same for the treatment of candidiaemia or empirical therapy in non-neutropenic patients in intensive care (see Sections I and V) (strong recommendation; moderate-grade evidence). The duration of treatment should be determined by the appropriateness of radiotherapy and clinical response (strong recommendation; low-quality evidence). IX. Does the respiratory isolation of Candida species require antifungal therapy? Candida growth from respiratory secretions usually indicates colonisation and rarely requires antifungal treatment recommendation; medium-quality evidence). X. What is the treatment for Candida invasive infections, including endocarditis and infections implantable in heart devices? What is the treatment for Candida myocarditic thing? Native valve endocarditis, lipid preparation AmB, 3-5 mg/kg per day, either flucytosine, 25 mg/kg 4 times daily, OR high doses of echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily) recommended for initial therapy (strong recommendation; low quality evidence). Step-down therapy with fluconazol, 400-800 mg (6-12 mg/kg) per day, is recommended for patients who are susceptible to Candida isolates, demonstrated clinical stability and cleared Candida into the bloodstream (strong recommendation; low quality evidence). Oral voriconazole, 200-300 mg (3-4 mg/ kg) twice a day, or posaconazole tablets, 300 mg per day, can be used as step-down therapy isolates that are susceptible to those agents but are not sensitive to fluconazole (poor recommendation; very poor quality evidence). Valve replacement is recommended; treatment should be continued for at least 6 weeks after surgery and for a longer period of time in perivalvular abscesses and other complications (strong recommendation; low-quality evidence). In patients who can not go through valve replacement, long-term suppression of fluconazole, 400-800 mg (6-12 mg/kg) per day if the isolate is sensitive, recommended (strong recommendation; low-quality evidence). For prosthetic valve endocarditis, the same antifungal regimen recommended for native valve endocarditis is recommended (strong recommendation; low-quality evidence). Chronic suppressive antifungal treatment fluconazol, 400-800 mg (6-12 mg/ kg) per day, is recommended to prevent recurrence (strong recommendation; low-quality evidence). What is the treatment for Candida infection implantable in heart devices? In the case of pacemaker and implantable heart defibrillator infections, the entire device should be removed (strong recommendation; medium-quality evidence). Antifungal therapy is the same as recommended for native valve endocarditis (strong recommendation; low quality evidence). For infections limited to generator pockets, 4 weeks of antifungal therapy is recommended after removal of the device (strong recommendation; low-quality evidence). In the case of infections affecting the ducts, antifungal treatment of at least 6 weeks is recommended after wiring removal (strong recommendation; low-quality evidence). For ventricular assist devices that can not be removed late, antifungal treatment is the same as recommended for native valve endocarditis (strong recommendation; low-quality evidence). Chronic suppressive therapy with fluconazol, if the isolate is sensitive, as long as the device remains in place recommended (strong recommendation; low-quality evidence). What is the treatment for Candida Suppurative Thrombophlebitis? Catheter removal and pruning and or resection of the vein, if feasible, recommended (strong recommendation; low-quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, OR fluconazole, 400-800 mg (6-12 mg) per day, or echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily) recommended at least 2 weeks after candidemia (if any) (strong recommendation; low quality evidence). Fluconazole 400-800 mg (6-12 mg/kg) step-down therapy per day should be considered in patients who initially responded to AmB or an echinocandin, are clinically stable and have fluconazol-sensitive isolates (strong recommendation; low-quality evidence). The dissension of the thrombus can be used as evidence to discontinue antifungal treatment if supported by clinical and breeding data (strong recommendation; low-quality evidence). XI. What is the treatment of Candida osteoarticular infections? What is the treatment of Candida Osteomyelitis? Fluconazol, 400 mg (6 mg/kg) per day, For 6-12 months or echinocandin (50-70 mg of caspofungin per day, 100 mg of micafungin or 100 mg of anidulafungin per day) for at least 2 weeks, then fluconazole, 400 mg (6 mg/kg) per day, recommended for 6-12 months (strong recommendation; low quality evidence). Lipid preparation AmB, 3-5 mg/kg per day for at least 2 weeks, followed by fluconazole, 400 mg (6 mg/ kg) per day, 6-12 months is a less attractive alternative (poor recommendation; low quality evidence). Surgical debridement is recommended in some cases (strong recommendation; low-quality evidence). What is the treatment for Candida septic arthritis? Fluconazole, 400 mg (6 mg/kg) daily, 6 weeks or one echinocandin (caspofungin 50-70 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily) for 2 weeks, followed by fluconazole, 400 mg (6 mg/ kg) daily, recommended for at least 4 weeks (strong recommendation; low quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, 2 weeks, then fluconazole, 400 mg (6 mg/ kg) per day, at least 4 weeks less attractive alternative (poor recommendation; low quality evidence). Surgical drainage in all cases with septic arthritis (strong recommendation; moderate-quality evidence). In the case of septic arthritis, which contains a prosthetic device, it is recommended to remove the device (strong recommendation; evidence of moderate quality). If the prosthesis device cannot be removed, chronic suppression with fluconazole, 400 mg (6 mg/kg) per day , if the isolate is sensitive, is recommended (strong recommendation; low-quality evidence). XII. What is the treatment of Candida endophthalmitis? What is the general approach to candida endophthalmitis? All patients with candidemia should have an dilated retinal examination, preferably by an ophthalmologist, in non-neutropenia patients during the first week of therapy to determine whether endophtomy is present (strong recommendation; low-quality evidence). Neutropenia patients delay in neutrophil recovery (strong recommendation; low-quality evidence). The degree of eye infection (chorioretinitis with or without macular contact, with or without vitritis) should be determined by an ophthalmologist (strong recommendation; low-quality evidence). Decisions on antifungal treatment and surgical intervention should be taken jointly by an ophthalmologist and infectious diseases doctor (strong recommendation; low-quality evidence). What is the treatment of Candida Chorioretinitis without Vitritis? fluconazole/voriconazole sensitive isolates, 800 mg (12 mg/kg), then 400-800 mg (6-12 mg/kg) or voriconazole, 400 mg (6 mg/kg) intravenous doses twice a day, 2 doses, then 300 mg (4 mg/kg) intravenous or oral twice daily (strong recommendation; low-quality evidence). Fluconazole/voriconazole-resistant isolates, liposomal AmB, 3-5 mg/kg intravenous daily with or without oral flucytosine, 25 mg/kg 4 times daily recommended (strong recommendation; low quality evidence). Macular impresity, antifungal agents such as above-mentioned PLUS intravitreal injection or AmB deoxycolate, 5-10 µg/ 0.1 mL sterile water, or voriconazole, 100 µg/0. 1 l sterile water or normal saline solution, to ensure a rapid high level of antifungal activity is recommended (strong recommendation; low quality evidence). The duration of treatment is at least 4-6 weeks, the final duration depending on the resolution of the lesions determined by repeated ophthalmic examinations (strong recommendation; low quality evidence). What is the treatment of Candida Chorioretinitis with Vitritis? The antifungal treatment detailed above is recommended for chorioretinitis without vitritis, intravitreal injection of b-deoxycolate am-hotericin B deoxycolate, 5-10 µg/0,1 mL sterile water or voriconazole, 100 µg/0,1 mL sterile water or normal saline solution (strong recommendation; low quality evidence). Vitrectomy should be considered to reduce the burden on organisms and allow the removal of fungal bowls, which are not available for systemic antifungal agents (strong recommendation; low-quality evidence). The duration of treatment should be at least 4-6 weeks, the final duration depends on the resolution of lesions, which is determined by repeated ophthalmic examinations (strong recommendation; low-quality evidence). XIII. What is the treatment of CNS candidiasis? For initial treatment, liposomal AmB, 5 mg/kg daily with or without oral flucytosine, 25 mg/kg 4 times daily recommended (strong recommendation; low quality evidence). After step-down therapy, the patient responded to initial treatment, fluconazole, 400-800 mg (6-12 mg/ kg) per day, recommended (strong recommendation; low-quality evidence). Therapy should be continued until all signs and symptoms, as well as CSF and radiological disorders, are eliminated (severe evidence of poor quality). Infected CNS devices, including ventriculostomy drains, bangs, stimulators, prosthetic reconstruction devices, and biopolymer wafers that deliver chemotherapy should be removed if possible (strong recommendation; low-quality evidence). In patients in whom the ventricular device cannot be removed, AmB deoxysolate can be injected into the chamber through the device between 0.01 mg and 0.5 mg in 2 mL 5% dextrez water (poor recommendation; low-quality evidence). XIV. What is the treatment of urinary tract infections due to Candida species? What is the treatment for asymptomatic Candiduria? Elimination of predisposing factors, such as inhabiting bladder cysts, is recommended whenever possible (strong recommendation; low-quality evidence). Treatment with antifungal drugs is NOT recommended, unless the patient belongs to a high-risk group; high-risk patients include neutropenic patients, infants with very low birth weight (<1500 g), and patients who have been subjected to urological manipulation (strong recommendation; low-quality evidence). Neutropenic patients and infants with very low birth weight should be treated as recommended for candidia (see sections III and VII) (strong recommendation; low-quality evidence). Patients who have had urological procedures should be treated daily with 400 mg (6 mg/kg) of oral fluconazole, or AmB deoxycolate, a daily dose of 0.3-0.6 mg/kg for a few days before and after the procedure (strong recommendation; low-quality evidence). What is the treatment of symptomatic Candida Cystitis? Fluconazol-sensitive organisms, oral fluconazole, 200 mg (3 mg/ kg) daily recommended for 2 weeks (strong recommendation; moderate-grade evidence). Fluconazol-resistant C. glabrata, AmB deoxycolate, 0.3-0.6 mg/kg daily 1-7 days OR oral flucytosine, 25 mg/kg 4 times a day 7-10 days recommended (strong recommendation; low quality evidence). For C. krusei, AmB deoxycolate, 0.3-0.6 mg/kg, is recommended for 1-7 days per day (strong recommendation; low-quality evidence). Removal of an indoor vesicular cystheter, if feasible, is highly recommended (strong recommendation; low-quality evidence). AmB deoxycolate bladder watering, 50 mg/ L of sterile water per day for 5 days, may be useful in the treatment of cystitis due to fluconazol-resistant species such as C. glabrata and C. krusei (poor recommendation; poor quality evidence). What is the treatment of symptomatic increasing Candida Pyelonephritis? Fluconazol-sensitive organisms, oral fluconazol, 200-400 mg (3-6 mg/kg) per day recommended for 2 weeks (strong recommendation; low-quality evidence). Fluconazol-resistant C. glabrata, AmB deoxycolate, 0.3-0.6 mg/kg daily for 1-7 days, with or without oral flucytosine, 25 mg/kg 4 times daily, recommended (strong recommendation; low quality evidence). For fluconazol-resistant C. glabrata, monotherapy with oral

flucytosin, 25 mg/kg 4 times a day for 2 weeks, (poor recommendation; low-quality evidence). For C. krusei, AmB deoxycolate, 0.3-0.6 mg/kg, is recommended for 1-7 days per day (strong recommendation; low-quality evidence). Elimination of urinary obstruction is highly recommended (strong recommendation; low quality evidence). In patients who have nephrostomic tubes or stents in place, it is recommended to remove or replace it if feasible (poor recommendation; low-quality evidence). What is the treatment of Candida urinary tract infection associated with fungal balls? Surgical intervention is highly recommended in adults (strong recommendation; low-quality evidence). The above-mentioned antifungal treatment of cystitis or pyelonephritis is recommended (strong recommendation; low-quality evidence). Watering nephrostomy tubes, if any, with AmB deoxycolate, 25-50 mg of 200-500 mL of sterile water, recommended (strong recommendation; low-quality evidence). XV. What is the treatment of vulvovaginal candidiasis? Treatment of uncompetized Candida vulvovaginitis, topical antifungal agents, no one agent is better for the other, recommended (strong recommendation; high-quality evidence). Alternatively, in the treatment of uncompetative Candida vulvovaginitis, a single 150 mg oral dose of fluconazole is recommended (strong recommendation; high-quality evidence). Severe acute Candida vulvovaginitis, fluconazol, 150 mg, given every 72 hours for a total of 2 or 3 doses, is recommended (strong recommendation; high-quality evidence). C. glabrata vulvovaginitis, which does not respond to oral azoles, topical intravaginal boric acid, is administered in one gelatin capsule, 600 mg daily, for 14 days is an alternative (strong recommendation; low quality evidence). Another alternative agent for C. glabrata infection is nystatin intravaginal suppositories, 100,000 units per day for 14 days (strong recommendation; low quality evidence). The third option for C. glabrata infection is topical 17% flucytosine cream alone or in combination with 3% AmB cream per day for 14 days (weak recommendation; low quality evidence). For recurrent vulvovaginal candidiasis, 10-14 days of induction therapy with topical agent or oral fluconazol, followed by fluconazole, 150 mg per week is recommended for 6 months (strong recommendation; high-quality evidence). XVI. What is the treatment of oropharyngeal candidiasis? Mild disease, clotrimazole troches, 10 mg 5 times a day, OR miconazol mucoadhesive tuple50 mg tablets over the surface of the mucous membrane of the dog fossa once a day 7-14 days recommended (strong recommendation; high quality evidence). Alternatives to mild disease include nystatin suspension (100,000 U/mL) 4-6 mL 4 times a day, OR 1-2 nystatin pastils (200,000 U each) 4 times a day, 7-14 days (strong recommendation; moderate quality evidence). For moderate to severe illness, oral fluconazole, 100-200 mg daily, recommended for 7-14 days (strong high-quality evidence). Fluconazole refrakter disease, itraconazole solution, 200 mg once a day OR posaconazole suspension, 400 mg twice a day for 3 days, then 400 mg daily, up to 28 days recommended (strong recommendation; moderate quality evidence). Alternatives for fluconazole-refractory disease include voriconazole, 200 mg twice daily, OR AmB deoxysole oral suspension, 100 mg/mL 4 times a day (strong recommendation; moderate quality evidence). Intravenous echinocandin (caspofungin: 70 mg loading dose, then 50 mg daily; micafungin: 100 mg daily; or anidulafungin: 200 mg load dose, then 100 mg daily) OR injecting AmB deoxycolate, 0.3 mg/kg per day, other alternative to refracter disease (weak recommendation; moderate-quality evidence). Chronic suppressive therapy is usually unnecessary. If fluconazole is recommended in patients with recurrent infection, 100 mg 3 times a week (strong recommendation; high-quality evidence). In HIV-infected patients, antiretroviral therapy is highly recommended to reduce the incidence of recurrent infections (strong recommendation; high-quality evidence). In the case of candidiasis associated with dentures, disinfection of the dentures is recommended in addition to antifungal therapy (strong recommendation; evidence of moderate quality). XVII. What is the treatment of candidiasis of the esophagus? Systemic antifungal treatment is required. Diagnostic examination of antifungal therapy is appropriate before carrying out an endoscopic examination (strong recommendation; high-quality evidence). Oral fluconazole, 200-400 mg (3-6 mg/kg) per day, recommended for 14-21 days (strong recommendation; high-quality evidence). In patients who do not tolerate oral therapy, intravenous fluconazole, daily 400 mg (6 mg/kg) or echinocandin (micafungin, 150 mg daily, caspofungin, 70 mg loading dose, then 50 mg daily, or anidulafungin, 200 mg daily) is recommended (strong recommendation; high quality evidence). A less preferred alternative for those who do not tolerate oral therapy amb deoxycolate is 0.3-0.7 mg/kg per day (strong recommendation; moderate quality evidence). Consider de-escalating oral treatment with fluconazol 200-400 mg (3-6 mg/ kg) per day if the patient is able to tolerate oral intake (strong recommendation; moderate quality evidence). Fluconazole refrakter disease, itraconazole solution, 200 mg daily, OR voriconazole, 200 mg (3 mg/kg) twice a day intravenous or oral, recommended for 14-21 days (strong recommendation; high-quality evidence). Alternatives to fluconazol-refrakter disease include echinocandin (micafungin: 150 mg per day; caspofungin: 70 mg filling dose, then 50 mg daily; or anidulafungin: 200 mg daily) for 14-21 days, OR AmB deoxycholate, 0.3-0.7 mg/kg daily, for 21 days (strong recommendation; high-quality evidence). Posaconazole suspension is 400 mg twice daily or 300 mg once a day for longer (poor recommendation; low-quality evidence). In patients who have recurrent esophagitis, chronic repressive treatment fluconazole, 100-200 mg three times a week is recommended (strong recommendation; high-quality evidence). In HIV-infected patients, antiretroviral therapy is highly recommended to reduce the incidence of recurrent infections (strong recommendation; high-quality evidence). In the first section, the panel summarizes background information on the subject. In the second phase, the Panel will ask questions about the treatment of candidiasis, evaluate the applicable clinical trial and observation data and make recommendations within the framework of the Classification of Evaluation, Development and Evaluation of Recommendations (GRADE) [2]. The following 17 questions were answered: What is the treatment for candidemia in nonneutropenic patients? Can central venous catheters be removed in non-neutropenic patients with candidemia? What is the treatment for candidia in neutropenic patients? What is the treatment for chronic disseminated (hepatosplenic) candidiasis? What is the role of empirical treatment in suspected invasive candidiasis nonneutropenic patients in the intensive care unit? Should prophylaxis be used to prevent invasive candidiasis in the intensive care unit setting? What is the treatment for neonatal candidiasis, including central nervous system infection? What is the treatment for intra-abdominal candidiasis? Does the respiratory isolation of Candida species require antifungal therapy? What is the treatment for Candida invascular infections, including endocarditis and infections implantable in heart devices? What is the treatment for Candida osteoarticular infections? What is the treatment of Candida endophthalmitis? What is the treatment of CNS candidiasis? What is the treatment of urinary tract infections due to Candida species? What is the treatment of vulvovaginal candidiasis? What is the treatment for oropharyngeal candidiasis? What is the treatment of candidiasis of the esophagus? Infections caused by Candida species are the main cause of diseases and mortality in humans, causing a diverse spectrum of clinical diseases, from superficial and mucous infections to invasive diseases associated with candidemia and matic organ lesions. As an organism, candidemia is one of the most common health-related bloodstream infections in U.S. hospitals, typically ranking as the third or fourth most common cause of health-related bloodstream infection. A recent multicentre point prevalence survey identified Candida species as the most isolated, healthcare-related bloodstream agent [4]. Among patients with candidemia and other forms of invasive candidiasis, non-albicancans Candida species account for approximately 50% of all relevant isolates, which has been continuous for more than a decade in many regions of the world [5-12]. The number of clinical candidiasis, candidiasis and invasive candidiasis received the most attention in clinical trials. Candidia can cause up to 47% mortality [5-13], and this is even higher among septic shock sufferers [14]. Many authors have demonstrated that mortality is closely linked to both therapy timing and resource control [14-19]. As a matter of fact, prior intervention with appropriate antifungal therapy and removal of contaminated central venous catheter (CVC) or draining of the infected substance usually have better overall results [14-19]. CVC is often linked to candidiaemia, but catheters are not always the source, especially for neutropenic patients who develop a common source of gastrointestinal tract. Most experts agree that thoughtful patient-specific treatment of CCs is critical to the overall treatment of infection [19]. Continued reliance on blood cultures, notoriously insensitive as markers of the disease, remains a major obstacle to early intervention. The development of reliable nonculture studies is crucial to provide an opportunity for previous intervention and more targeted antifungal therapy among a large number of patients for whom traditional blood cultures are insensitive or give untimely results [20]. The distribution of species is also a major challenge for all forms of candidiasis and there is significant geographical, medium and even unit variability in the occurrence of pathogenic Candida species [8-12]. Indeed, candidiasis is not one but several diseases, each Candida species presents its own unique characteristics with respect to tissue tropism, a willingness to cause invasive disease, virulence, and antifungal sensitivity. Knowing the ratio of local epidemiological and antifungal resistance is critical in making informed therapeutic decisions while awaiting culture and sensitivity data. Despite the overall robust nature of randomized controlled trials for the treatment of candidemia and other invasive candidiasis [21-34], one study did not demonstrate a clear superiority of one therapeutic agent over another. Careful analysis of these clinical data sometimes leads to conflicting conclusions. For example, the use of amphotericin B (AmB) and fluconazole is at least as effective as the use of higher doses of fluconazole alone (800 mg per day) in patients with candidemia [22], but in current practice this combination has little role, especially as echinocandins are such a safe and effective alternative. Similarly, voriconazole is just as effective as the strategy of sequential AmB and fluconazole for candidemia, but few would choose voconazole in this setting, as it has few benefits and potentially greater toxicity associated with using this drug than other therapies [23]. Echinocandins in most episodes of candidiaemia and candidia preferred preferred candidiasis, except for the central nervous system (CNS), eye, and urinary tract infections due to these organisms. This preference is based on a tendency towards better results based on a strong safety profile, comfort, early fungiciter activity, data from each study and a combined analysis of candidemia studies [19, 25] and the appearance of azol-resistant Candida species. The recent emergence of multi-resistant Candida species further complicates the selection of antifungal therapy in the near future [10, 12, 35-38], as there are no good forward-looking data to guide the therapy. There is a wealth of clinical data generated from large randomized clinical trials of candidemia, Candida esophagitis, oropharyngeal candidiasis, and prophylaxis studies in specialized populations, such as patients in intensive care units (IcUs), newborns, and selected transplant recipients, and these studies have led to important insights into optimal therapeutic approaches in these vulnerable populations. For those with less common manifestations of the disease, such as osteomyelitis, endophthalmitis, and infectious endocarditis, treatment recommendations are largely based on extrapolation from randomized trials in patients with other diseases, small retrospective series, and anecdotal reports. It is therefore critical to continuously evaluate this data in order to make timely recommendations for the treatment of patients with these less common forms of candidiasis. Panel composition The latest version of the Guidelines of the American Society for Infectious Diseases (IDSA) on the treatment of patients with candidiasis was published in 2009 [1]. For this update, the IDSA Standards and Practice Guidelines Committee (SPGC) convened a multidisciplinary panel of 12 experts to treat patients with candidiasis. The panel has 12 members of IDSA, and 11 adult infectious disease doctors and 1 pediatric infectious disease doctor. Each panel member was selected on the basis of their expertise in clinical and/or laboratory mycology, in particular candidiasis. The members of the Literature Review and Analysis Panel were commissioned to review the latest literature on at least 1 topic, evaluate the evidence, determine the strength of the recommendations and develop written evidence to support these recommendations. PubMed, which includes Medline (1946 to the present), was looking to identify relevant studies on candida guidelines for PICO (population/patient, intervention/indicator, comparative/control) issues. Search strategies have been developed and built by 2 independent health sciences librarians at the Health Sciences Library System, University of Pittsburgh. Librarians developed search strategies for each PICO question using PubMed's scripting language and corresponding search fields. Az Medical topic headers (MeSH) were used for the main search concepts of PICO questions. Used. in all languages and in all publication years. The first searches were established and confirmed by wedges prepared between August and November 2013 by commission chaires of the guidelines and team leaders. Searches were finalised and delivered between the end of November 2013 and January 2014. After conducting literary searches, the authors continued to review the literature and added the relevant articles as needed. Process Overview The panel met twice in person and made a number of conference calls over 2 years. The Panel reviewed and discussed all recommendations, their strength and the quality of evidence. The contradictions have been discussed and resolved and all final recommendations represent the consensus opinion of the whole body. For the final version of these guidelines, the Panel reviewed all sections as a group. Evidence review: GRADE method grade is a systematic approach to the development of the Guidelines, described in detail elsewhere [2, 39]. IDSA adopted GRADE in 2008. In grade, the guidance body assigns each recommendation with a separate rating on the basic quality of the evidence supporting the recommendation and the strength of the preparation of the recommendation (Figure 1). Data from randomised controlled trials start as high quality and data from observational studies start with low quality. However, the panel may assess whether the specific characteristics of the data justify a reduction or increase in the classification of evidence and grade provides guidance on how these factors should be considered [39]. The strength assigned to the recommendation reflects, in particular, the trust of the Board that the benefits of following the recommendation are likely to outweigh the potential harm. While the quality of evidence is an important factor in choosing the imperete strength of the recommendation, it is not prescriptive. Guidelines and conflicts of interest The panel of experts complied with IDSA's conflict of interest policy, which requires the disclosure of any financial or other interest that may constitute actual, potential or manifest conflict. The panel members received idsa's declaration of conflict of interest and were asked to identify contacts with companies that could develop products that could be affected by the publication of the guidelines. They asked for information on employment, advice, share ownership, fees, research funding, expert testimony and membership of corporate advisory committees. Decisions have been taken on a case-by-case basis as to whether the role of the individual should be limited as a result of conflict. Lists any conflicts of interest in the Confirmations section. Consensus development based on evidence The Panel received feedback from 3 external experts. The guidelines were adopted by MSG, The Academy of Pediatrics (AAP) and the Pediatric Infectious Diseases Society (PIDS) have reviewed and approved it. The guidelines have been reviewed and approved by the IDSA SPGC and IDSA Board of Directors before distribution. Review dates At annual intervals, panel chaires are invited to contribute to the need to update the guidelines on the basis of an examination of the current literature. The IDSA SPGC takes this input into account and determines the need and timing of the upgrade. Where appropriate, the entire body or part there of it shall be convened to discuss possible changes. Antifungal drugs Pharmacological considerations during the therapy of candidiasis Systemic antifungal drugs, which have been shown to be effective in the treatment of invasive candidiasis, include 4 main categories: polyenes (amphotericin B [AmB] deoxycolate, liposomal AmB, AmB lipid complex [ABLC], and amphotericin B colloidal dispersion [ABCD, not available in the United States]), triazole (fluconazole, itraconazole, voriconazole, and posaconazole), echinocandins (caspofungin, anidulafungin, and micafungin), and flucytosin. Data from a recently completed clinical trial comparing echinocandin for invasive candidiasis with isavukonazol are currently not available. Clinicians should be familiar with efficiency optimisation strategies by understanding the relevant pharmacokinetic properties. Amphotericin B Most experience amB in the deoxycholyate formulation. Three lipid formulations of AmB have been developed and approved in humans: ABLC, ABCD, and Liposomal AmB. These substances have the same activity spectrum as AmB deoxycolate, but daily dosing regimens and toxicity profiles differ for each agent. The 3 lipid preparation AmB agents have different pharmacological properties and rates of treatment-related side effects and cannot be replaced without careful consideration. In this document, the reference to amb, without contesting a particular dose or other form, shall be considered as a reference to the general use of any of the AmB preparations. For most forms of invasive candidiasis, the typical intravenous dose of AmB deoxycolate is 0.5 to 0.7 mg/kg per day, but invasive Candida infections caused by less susceptible species such as C. glabrata and C. krusei should take into account high doses such as 1 mg/kg. The typical dose of lipid preparation AmB is 3-5 mg/kg per day when used for invasive candidiasis. Nephrotoxicity is the most common serious adverse effect associated with AmB deoxycolate therapy, resulting in acute kidney damage and electrolyte-atrophying tubular acidosis in the majority of patients in up to 50% of recipients [40, 41]. AmB lipid preparations are more expensive than AmB deoxycolate, but each has significantly less nephrotoxicity [42, 43]. Most observers agree that lipid formulations, with the exception of ABCD, provoke fewer infusion-related reactions than AmB deoxycolate. In clinical trials, no the effect of pharmacokinetics and differences in toxicity of AmB lipid preparations. We are not aware of any forms, forms of candidiasis amb formulations are better than AmB deoxysolate in terms of clinical efficacy. In addition, we are not aware of a situation in which lipid preparations should not be used, except for urinary tract infections, because of decreased kidney excretion of these preparations. Animal model studies suggest a pharmacokinetic and therapeutic benefit for liposomal AmB in cns [44]. Data on nephrotoxicity induced by AmB deoxycolate are associated with a 6.6-fold increase in mortality, which led many clinicians to use AmB lipid preparations in proven or suspected candidiasis, especially in patients in high-risk environments such as ICU [45]. Triazole fluconazole, itraconazole, voriconazole, posaconazole and a new expanded spectrum triazole, isavukonazole, have similar activity against most Candida species [46-51]. Each azola has less activity against C. glabrata and C. krusei than against other Candida species. All azol antifungal agents inhibit cytokrome P450 enzymes to some extent [52]. Thus, clinicians should carefully consider the effect of the patient's medication when adding or removing azol. In large clinical studies, fluconazole has shown a similar efficacy to AmB deoxycolate in the treatment of candidemia [21.22] and can also be considered standard therapy for oropharyngeal, esophageal and vaginal candidiasis and urinary tract infections [53,54]. Fluconazole is readily absorbed, with approximately 90% of the concentrations achieved by intravenous use due to its oral bioavailability [55]. Its absorption does not affect food consumption, stomach pH, or the condition of the disease. Fluconazole is the highest penetration of triazole into the cerebrospinal fluid (CSF) and the glass body and reaches a concentration of >70% of those in the serum [56-59]. For this reason, it is often used to treat cns and intraocular Candida infections. Fluconazole achieves a urine concentration of 10 to 20 times serum concentration and is thus the preferred treatment option for symptomatic cystitis [59]. In patients with invasive candidiasis, fluconazol should be administered at an average load dose of 800 mg (12 mg/kg), followed by an average daily dose of 400 mg (6 mg/kg). Higher dose levels (800 mg per day, 12 mg/kg) are often recommended for the treatment of susceptible C. glabrata infections, but this has not been validated in clinical trials. Elimination of fluconazole is almost completely renal; therefore, dose reduction is required in patients with creatinine clearance < 50 mL/min creatinine clearance. Itraconazol is available only in oral preparations. It has not been studied well for invasive candidiasis and is generally reserved for patients with mucous candidiasis, especially those who have experienced a treatment error with fluconazol [60]. Gastrointestinal absorption varies among patients and is greater for oral solution than for Histamine receptor antagonists and proton pump inhibitors result in a decrease in the absorption of the capsule preparation, while acidic drinks increase absorption [61]. The use of the capsule formulation with food increases absorption, but the oral solution is better absorbed on an emptying (62). Oral preparations are administered to adults 200 mg 3 times a day for 3 days, followed by 200 mg once or twice a day thereafter. Voriconazole demonstrated its effectiveness in both mucous membrane and invasive candidiasis [23, 63]. Its clinical use is primarily for single oral treatment in patients with C. krusei and fluconazole-resistant, voriconazole-sensitive C. glabrata infection. CSF and glass body concentrations are >50% of serum concentrations, and voriconazole has been shown to be effective in series for such sites of infection [64-66]. Voriconazole does not accumulate in an active form in the urine and therefore should not be used for urinary candidiasis. Oral bioavailability of voriconazole is excellent and does not affect the pH of the stomach, but decreases when the drug is administered with food [67, 68]. In adults, the recommended oral dosing regimen for candidiasis includes a load dose of 400 mg (6 mg/kg) twice a day for 2 doses followed by 200-300 mg (3-4 mg/kg) twice a day. Intravenous voriconazole complexed with a cyclodextrin molecule; A maintenance dose of 3-4 mg/kg is recommended every 12 hours after a dose of 2.6 mg/kg every 12 hours. Due to the potential for accumulation of cyclodextrin and possible nephrotoxicity in patients with significant renal dysfunction, intravenous voriconazole is not currently recommended in patients with creatinine clearance <50 mL/min. However, a retrospective study of the use of intravenous voriconazole in patients with different levels of renal function below this limit identified no toxic effects, which alleviated some of these concerns [69, 70]. Oral voriconazol does not require a dosing adjustment for renal failure, but it is the only triazole that requires a reduction in dosage in patients with mild to moderate liver damage [71]. Common polymorphisms in the gene coding for the primary metabolic enzyme voriconazole result in a wide variability in serum levels [72]. Drug-drug interactions are common with voriconazole and should be taken into account when taking and discontinuing treatment with this compound [52]. Voriconazole has not been systematically studied in fluconazole-resistant Candida species and use is not currently recommended with the exception of C. krusei. All triazoles may have uncommon side effects. However, several effects are unique to voriconazole or are more commonly associated with higher voriconazole concentrations, including liver injury, visual side effects, photosensitivity, periostitis, and cns side effects [73-75]. Posaconazole has no indication for primary candidiasis therapy. It shows the in vitro Candida species that are similar to voriconazole, but clinical data are insufficient to provide an evidence-based recommendation for the treatment of candidiasis other than oropharyngeal candidiasis [76]. Posaconazole is currently available as an extended release tablet, oral suspension and intravenous solution. The tablet preparation, which is given to 300 mg twice a day for 2 doses, then results in a predictable serum concentration of 300 mg per day and excellent drug exposure and requires only once daily dosing [77,78]. The bioavailability of oral suspension is unpredictable [79-81]. Intravenous posakonazole is given 300 mg twice a day in 2 doses, followed by 300 mg daily. Isavukonazole is a recently approved expanded triazole antifungal with excellent in vitro activity against Candida species. Preliminary analysis of the recently completed large international double-blind study comparing isavuconazol to invasive candidiasis echinocandin suggests that isavuconazole did not meet the criteria for noninferiority (personal communication, Astellas US). Echinocandins Caspofungin, anidulafungin and micafungin are only available as parenteral products [82-84]. The minimum inhibitory concentration of echinocandins (NIC) is low for most Candida species, including C. glabrata and C. krusei [48-50]. However, a recent treatment error related to resistant strains of C. glabrata [85, 86] has been received. Candida parapsilosis demonstrates congenital higher NICs in echinocandins than most other Candida species, raising concerns that C. parapsilosis may be less responsive to echinocandins. All of these agents have been studied for the treatment of esophageal candidiasis [24, 87, 88] and invasive candidiasis [25-34], all of which have been shown to be effective in these situations. Recent pooled analyses of almost exclusively non-neneudontenenic patients in randomised invasive candidiasis treatment studies suggest a survival benefit associated with initial echinocandine therapy [19]. All echinocandin has minimal adverse effects. Pharmacological properties are very similar in adults and are all administered intravenously once a day [82-84]. Echinocandins achieve therapeutic concentrations at all contagion points except eyes, CNS and urine [59]. The main pathway to elimination is non-enzymatic degradation. None of the echinocandins require dose adjustment due to kidney failure or dialysis. Both caspofungin and micafungin go through minimal liver metabolism, but neither drug is the main carrier of cytokrome P450. Caspofungin is the only echinocandin for which dose reduction is recommended in patients with moderate to severe liver dysfunction. The usual intravenous dosing regimen for invasive candidiasis is as follows: caspofungin: 70 mg, then 50 mg daily filling; anidulafungin: 200 mg, then 100 mg daily; and micafungin: 100 daily (no load dose required). Flucytosine (flucytosine) it exhibits widespread antifungal activity against most Candida species, with the exception of C. krusei. The compound is available in the United States only as an oral formulation. The drug has a short half-life (2.4-4.8 hours) and is usually administered at a dose of 25 mg/kg 4 times daily to patients with normal kidney function. Flucytosin shows this excellent absorption after oral application (80%-90%), and most of the drug is excreted unchanged (microbiologically active) in the urine [89.90]; in patients with renal dysfunction, dose modification is required [91,92]. The compound exhibits high penetration into the cns and eyes. Concentration-dependent toxicity results in bone marrow suppression and hepatitis. Flucytosin is usually given in combination with another antifungal agent, as monotherapy had a high rate of resistance [93]. The most common use of flucytosine in Candida infection is in combination with AmB in patients with more refractory infections such as Candida endocarditis, meningitis or endophthalmitis. It is occasionally used to treat isconazol-resistant candidiasis due to fluconazol-resistant C. glabrata [94]. Paediatric dosing There are significant differences in pharmacokinetics of antifungal drugs between adult and paediatric patients, and in pediatric patients, data on giving are limited. The pharmacological properties of antifungal agents in children and infants have been reviewed in detail [95]. The optimal dose of AmB deoxycolate has not been clearly defined; usually a dose of 1 mg/kg is used [96-98]. The maximum daily concentrations of safety, efficacy, sub-curve area and ABLC of 2-5 mg/kg in adults and children are similar [99]. The pharmacokineticism of liposomal AmB in neonates and children suggests that both volume and clearance are affected by weight [100]. Flucytosin clearance is directly proportional to the glomerular screening rate and infants with very low birth weight may accumulate high plasma concentrations due to poor kidney function due to immaturity [101]. Thus, the use of flucytosine in this group of patients is opposed without careful monitoring of serum drug levels. The pharmacokineetic of fluconazole varies depending on age, and the drug is quickly cleared in children. Thus, new misdeeds and children need a daily dose of 12 mg/kg of fluconazole [102-105]. The pharmacokinetica of Voriconazole varies widely in children [106-108]. In order to achieve plasma exposure similar to that of adults receiving 4 mg/kg every 12 hours, a load dose of 9 mg/kg intravenous voriconazole is recommended twice a day, followed by 8 mg/kg twice a day. The recommended oral dose is 9 mg/kg twice a day (maximum dose 350 mg) [95,107]. There are no data on the dosing of voriconazole in children <2 years of age, and there are no paediatric studies that indicate pharmacokinetic use of the intravenous product, suspension through the posakonazol tabletta. Caspofungin és micafungin által jóváhagyott us Food and Drug Administration (FDA) gyermekek számára. A caspofungin-ok beadatása a testfelületen, nem pedig a súlyon alapul. A gyermekeknél történő adagolás 70 mg/m2 betöltődadag, amelyet 50 mg/m2/nap követ. Előzetes vizsgálatok arra utalnak, optimális adag kaszpofungin neonátok 25 mg/m2/nap. Az invazív candidiasisra vonatkozó micafunginra vonatkozó jelenlegi ajánlás 2 mg/kg/nap, és 5 mg/L gyermekeknél 4 mg/kg/nap- ra lehet <40 kg.= the= optimal= dose= of= micafungin= in= neonates= is= unknown,= but= likely= to= be= 10= mg/kg/day= or= greater= [109].= anidulafungin= should= be= dosed= at= 1.5= mg/kg/day= for= neonates= and= children= [110–112].= considerations= during= pregnancy= amb= is= the= treatment= of= choice= for= invasive= candidiasis= in= pregnant= women= [113].= fluconazole,= itraconazole,= posaconazole,= and= isavuconazole= should= be= avoided= in= pregnant= women,= especially= those= in= the= first= trimester,= because= of= the= possibility= of= birth= defects= associated= with= their= use.= voriconazole= is= contraindicated= during= pregnancy= because= of= fetal= abnormalities= observed= in= animals.= there= are= few= data= concerning= the= echinocandins;= thus ,= their= use= is= cautioned= during= pregnancy.= flucytosine= is= contraindicated= during= pregnancy= because= of= fetal= abnormalities= observed= in= animals.= therapeutic= drug= monitoring= therapeutic= drug= monitoring= (tdm)= for= itraconazole,= voriconazole,= posaconazole,= and= flucytosine= has= been= shown= to= be= useful= for= optimizing= efficacy= and= limiting= toxicity= in= patients= receiving= therapy= for= a= variety= of= invasive= fungal= infections,= including= mucosal= and= invasive= candidiasis= [114].= the= basis= for= tdm= is= widely= variable= concentrations= among= patients= and= a= strong= relationship= between= concentration= and= efficacy= and/or= toxicity.= for= itraconazole,= when= measured= by= high-pressure= liquid= chromatography= (hplc),= both= itraconazole= and= its= bioactive= hydroxy-itraconazole= metabolite= are= reported,= the= sum= of= which= should= be= considered= in= assessing= drug= levels.= treatment= success= has= been= associated= with= concentrations= ≥1= mg/l= and= toxicity= with= concentrations=>emelkedni. A felnőttek nemlineáris farmakokinetikája és az anyagcsere genetikai különbségei miatt a szérum vorikonazol koncentrációban mind az intrapatient, mind a betegek közötti variabilitás fennáll [115–118]. A voriconazol- t kapó betegeknél megfontolandó a TDM- kezelés, mivel magasabb szérumkoncentrációk mellett gyógyszertoxicitást figyeltek meg, és alacsonyabb koncentrációban csökkent klinikai választ figyeltek meg [117, 118]. A kémiai onkonazol terápiás mélyponti koncentrációs ablaka 1–5,5 mg/l. Kevés adat áll rendelkezésre a pozakonazol hatékonyságának optimalizálására szolgáló specifikus koncentráció alátámasztására. A flucytosine monitorozást elsősorban a összefüggő toxicitás megelőzésére alkalmazzák. Csúcskoncentrációk <100 mg/L are recommended to avoid the predictable liver and bone marrow effects [119]. Antifungal Susceptibility Testing mg/l= are= recommended= to= avoid= the= predictable= liver= and= bone= marrow= effects= [119].= antifungal= susceptibility= testing=></100 mg/L are recommended to avoid the predictable liver and bone marrow effects [119]. Antifungal Susceptibility Testing > </40> </40> efforts to develop standardised, reproducible and relevant sensitivity testing methods for fungi have resulted in the development of the methodology of the M27-A3 Institute of Clinical and Laboratory Standards (CLSI) and the European Committee for Antimicrobial Sensitivity Tests (EUCAST) for yeast sensitivity testing [120]. Interpretative breakpoints on sensitivity take into account MIC, pharmacokinetic/pharmaco-pharmacolymatic data and animal model data. They shall be reported for each species. For most, but not all, drugs, breakpoints were established for the 5 most common Candida species [47, 50, 121, 122] (Table 1). In many cases, clinical breakpoints decreased to the one used earlier. For example, the previous Candida clinical breakpoint for fluconazole ≤8 mg/L. By the new interpretation, the susceptible value for albicans ≤ reduced to 2 mg/l. For C. glabrata, there is no breakpoint suitable for sensitivity to fluconazole, itraconazole, posaconazole or voriconazole (Table 1). If no clinical breakpoint has been established, an epidemiological limit value (ECV) based on an examination of the distribution of our mycoic within the species may be used. ECV is an MIC value that does not include non-wild strains, namely isolates likely to contain resistant mutants [50, 123]. The addition of the ECV method is particularly useful for detecting the appearance of resistance in Candida species in an institution. Candida's sensitivity to the currently available antifungal agents can usually be calculated if the species of infectious isolate is known. Currently, antifungal resistance to C. albicans is uncommon. However, individual isolates may not necessarily follow this general pattern [124]. Recent surveillance studies suggest that triazol resistance among C. glabrata isolates has increased to such an extent that, in the absence of a sensitivity test, it is difficult to rely on these drugs for therapy [12, 125, 126]. A similar trend was observed for a smaller proportion of C. glabrata isolates and echinocandins [35, 85, 125]. Sensitivity studies in other Candida species are less clear, although resistance between C. tropicalis and C. parapsilosis has been reported from third-degree care facilities that use extensive antifungal drugs [127, 128]. Due to these trends, sensitivity testing is increasingly used to control the treatment of candidemia and invasive candidiasis. Diagnosis of Candidiasis cultures of blood or other samples collected in sterile conditions has long been considered diagnostic gold standards for invasive candidiasis. Nonculture diagnostic tests such as antigen, antibody or β-D-glucan diagnostic tests, and polymerase chain reaction (PCR) are now put into clinical practice by cultures If used and interpreted judiciously, these studies have shown that several patients with invasive candidiasis have been direct antifungal treatment. However, in order to fully achieve the benefits of combining culture and nonculture tests, clinicians should carefully consider the types of invasive candidiasis, understand the strengths and limitations of each study and interpret the test results in the clinical environment. The use of cultures in the diagnosis of invasive candidiasis Includes invasive candidiasis 3 entities: candidemia in the absence of deep-rooted candidiasis, candidemia associated with deep-rooted candidiasis and deep-rooted candidiasis in the absence of candidemia [20]. The distribution of these entities is likely to vary between the centers; in balance, the data suggest that the size of the groups is approximately equal [129]. The overall sensitivity of blood cultures to the diagnosis of invasive candidiasis is roughly 50% [20]. The detection limit for blood cultures ≤1 colony forming unit/mL [130, 131]. The limit of detection of cultures is at or below the PCR [132-135]. As such, blood cultures should be positive for the vast majority of active Candida bloodstream infections. These can be negative for extremely low levels of candidiaemia, intermittent candidiaemia, deep-rooted candidiasis, which persists after sterilization of the bloodstream, or in the absence of candidemia in deep-rooted candidiasis resulting from direct inoction of Candida. Blood cultures are limited by slow lead times (median time to positivity of 2-3 days, 1 to ≥7 days) and the fact that they can become positive relatively late during the course of the disease [130, 136]. Tissues or fluid cultures extracted from infected sites during deep-seated candidiasis also show poor sensitivity (often <50%) and slow lead times and invasive sampling procedures which are dangerous or may be contra-ed due to the underlying disease [137]. Antigen and antibody detection candida antigen and anti-Candida antibody detection has gained greater acceptance in Europe than in the United States. In general, the detection of antigen is limited by rapid clearance from the bloodstream [138]. Concerns have been raised about the reliability of antibody detection in immunosuppressive hosts, but the studies performed well in patients with neutropenia and cell-mediated immunedes (including those receiving hematoma cell and solid organ transplants) [138,139]. Responses to specific antigens grating immunoglobulin G (IgG) typically performed better than those of immunoglobulin M (IgM), suggesting that many patients respond to amnesty by amnesty or carry out a continuous subclinical tissue invasion [139]. The best studied study is a combined manmanan/antimannan antibody test currently authorised in Europe, but not in the United States (Platelia Candida Ag and Ab; Bio-Rad). One study in 14 the sensitivity/specificity of invasive candidiasis diagnosis of manmannan and antimannan IgG was 58% /93% and 59%/83% each [140]. A A 83% and 86% had the best performance for C. albicans, C. glabrata and C. tropicalis infections. In a candidemia study, at least one study tested positive for blood culture in 73% of patients [141]. In a hepatospleniccandidiasis study, at least one study tested positive for radiological changes in 86% of patients [142]. This study is not widely used in the United States, and the role of the diagnosis and treatment of invasive candidiasis is unclear. β-D-Glucan detection of β-D-glucan is a cell wall constituent of Candida species, Aspergillus species, Pneumocystis jiroveci, and a number of other fungi. Serum β-D-glucan test (Fungus; Associates of Cape Cod, East Falmouth, Massachusetts) have approved the FDA as a supplement to cultures for the diagnosis of invasive yeast infections. True-positive results are not specific to invasive candidiasis, but rather suggest the possibility of invasive fungal infection. For this reason, in patient populations that are also at risk of invasive mold infections, such as he ha ha ha ha haemia cell transplant recipients, β-D-glucan offers a theoretical benefit over several narrow trials of candidiasis. β-D-glucan detection is able to identify cases of invasive candidiasis in the days before positive blood cultures and shorten the time to initiation of antifungal treatment [143]. Prophylactic or empirical antifungal treatment is likely to affect test performance. On the one hand, antifungal agents may reduce diagnostic sensitivity [144-146], but a decrease in β-D-glucan levels may also be related to responses to antifungal therapy [147]. In meta-analyses of β-D-glucan studies, the overall sensitivity and specificity of the diagnosis of invasive candidiasis were 75%-80% and 80% [144-146]. A number of questions complicate the interpretation of this data, including uncertainties about the best cutoff value for a positive result, the number of positive tests required to establish a diagnosis, and the optimal timing and frequency of tests among at-risk patients. There is significant heterogeneity between the studies on how these issues are handled, as well as patient and control populations, the extent and type of fungal pathogens targeted, invasive candidiasis disease entities, candida species distribution, previous antifungal use, specific β D-glucan studies used, and other aspects of study design and statistical interpretation. The main β-D-glucan diagnosis is the possibility of poor specificity and false positivity, which can be particularly problematic in patient populations for which nonculture diagnostics would be most useful. For example, false positive results are rare in healthy controls, but are definitely more common among patients in intensive care [148]. The causes of false positivity include other systemic infections, such as gram-positive and bacteriemia, certain antibiotics such as intravenous amoxicillin clavulanate (not available in the United States), hemodialysis, fungal fungal receipt of albumin or immunoglobulin, surgical gauze or other glucan-containing substances, and mucositis or other disturbances of the gastrointestinal mucosa [149-154]. The specificity of β-D-glucan can be improved if successive positive results are prescribed instead of a single result, but false positivity remains a significant limitation if the factors listed above are common in the population studied. An extreme example is the sensitivity/specificity of lung transplant patients and the positive and negative predictive values of routine observation β-D-glucan studies were 64%/9% and 14%/50% [155]. Furthermore, 90% of patients had at least β-D-glucan results. Therefore, the study will be most useful if it is directed at subgroups of patients whose clinical course of treatment or risk factors indicate particularly invasive candidiasis or other fungal infections. No role in the diagnosis of invasive candidiasis β-D-glucans in samples other than serum has been established. Csf β-D-glucan testing was 100% and 95% and 95% to 98%, with detection of non-Candida fungal central ns infections [156,157] β-D-glucan was highly sensitive and specific in the rabbit model of hematogen C. albicans meningoencephalitis [158]. Limited data suggest that positive predictive values of β-D-glucan in bronchoalveolis lavage fluid are poor for the diagnosis of fungal pneumonia [159]. Case reports are being prepared on the examination of samples collected from other sites of invasive Candida infection [160]. Limited data are available on the usefulness of β-D-glucan study in children [161]. The optimal β-D-glucan study in children is not known. In studies in uninfected immunocompetent individuals, the average β-D-glucan level is slightly higher in children than in adults [162]. Currently, it is not recommended β-D-glucan study guide pediatric clinical decision making. Polymerase chain reaction Candida PCR shares a number of potential benefits and β-D-glucan detection. Compared to cultures, PCR studies of different blood fractions have been shown to shorten the time to diagnosis of invasive candidiasis and initiation of antifungal treatment [134, 135]. The overall sensitivity and specificity of PCR for suspected invasive candidiasis in a recent meta-analysis was 95% and 92% respectively [134]. For probable invasive candidiasis, the sensitivity of PCR and blood cultures was 85% and 38%. The effect of antifungal drugs on diagnostic sensitivity was unclear. Data in candida-colonized patients were surprisingly limited, but there was a trend towards lower specificity. One of the main limitations of PCR tests is the lack of standardized methods and multicentre validation of test performance. A multicentre U.S. study of a standalone tool which amplifies and detects Candida DNA by PCR and T2 (T2 Biosystems, Lexington, Massachusetts) completed [163]. This study is FDA approved, but the role of early diagnosis and treatment of candidemia remains unclear until more data is available. PCR has potential benefits over β-D-glucan or antigen antibody tests, including the ability to identify species, the detection of molecular markers of drug resistance and multiplex formatting. In Europe, a full-blooded multiplex real-time PCR study (SeptiFast, Roche) looked at 19 bacteria and 6 fungi (C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei and Aspergillus fumigatus) in a number of studies with sepsis and neutrophic fever. In one study, the sensitivity of the study among patients with candidiasis was 94%; the only negative result was C. famata candidemia [164]. The role of PCR in the examination of samples other than blood cannot be established. Nonculture Diagnostic Testing for Blood Culture-Negative invasive candidiasis The vast majority of studies looked at nonculture diagnostics in the setting of candidemia. More limited data on deep-rooted candidiasis show how these studies can identify cases that are not currently oated by blood cultures. In a one-center study of prospective enrolled patients, the sensitivity/specifics of the fungus β-D-glucan study and the real-time quantitative PCR study (ViraCor-IBT, Lee's Summit, Missouri) of invasive candidiasis were 56%/73% and 80%/70%, respectively [132]. More importantly, blood cultures, β-D-glucan testing and sensitivity of PCR samples in deep-rooted candidiasis (mostly abdominal candidiasis) were 21%, 67% and 88%. The combination of positive blood culture β-D-glucan test showed a sensitivity of 79% to invasive candidiasis; positive blood culture or positive PCR sample was 98%. In a second study of serum β-D-glucan studies, Candida score (a predictive score of invasive candidiasis based on clinical parameters and burden of Candida colonization), and candida colonization indices (predictive scores based on load colonization) among prospective enrolled patients who are in surgical IUS 2 hospitals and who are at particular risk of abdominal candidiasis [143]. 2 consecutive positive β-D-glucan result sensitivity/specificity was 65% /78%. In contrast, the sensitivity of the blood cultures was only 7%. In addition to the identification of cases omitted by blood cultures, the β-D-glucan study was a positive median 5 and 6 days before the start of positive abdominal cultures and antifungal treatment, respectively. Candida scores and colonization indices were similar in sensitivity to β-D-glucan, but specificities were poorer (≤43%). In these studies, the interpretation of specificity was complicated by the fact that negative controls invasive candidiasis. Therefore, it is not clear whether the positive test results for controls were false positive (as defined in the studies) or whether they were genuine positive because of ahasis and poor sensitivity of the blood cultures. Indeed, this is a central challenge in evaluating new diagnostics for invasive candidiasis: How can test performance be accurately measured if the gold standard is inadequate? I. What is the treatment for Candidemia in nonneutropenic patients? Recommendations Echinocandin (caspofungin: 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: 200 mg, then 100 mg daily loading) is recommended as an initial therapy (strong recommendation; high-quality evidence). Fluconazole, intravenous or oral, 800 mg (12 mg/ kg) load dose, followed by 400 mg (6 mg/ kg) per day is an acceptable alternative to echinocandin as an initial therapy for selected patients, including those who are not in critical condition and who are not considered likely to be a fluconazol-resistant Candida species (strong recommendation; high-quality evidence). A study of azol sensitivity is recommended in all bloodstreams and other clinically significant Candida isolates. Consideration should be given to examining echinocandin sensitivity in patients who have previously been treated with echinocandin and among those with C. glabrata or C. parapsilosis (strong recommendation; low-quality evidence). The transition from echinocandin to fluconazole (usually within 5-7 days) is recommended for patients who are clinically stable, have fluconazol-sensitive isolates (e.g. albicans.C and negative repeated blood cultures after initiation of antifungal treatment (strong recommendation; moderate quality evidence). In the case of infection with C. glabrata, the transition to higher doses of fluconazole (12 mg/kg) daily or voriconazole 200-300 (3-4 mg/kg) twice a day should only be considered in patients with fluconazole sensitivity or voriconazole-sensitive isolate (strong recommendation; low-quality evidence). Lipid preparation amphotericin B (AmB) (3-5 mg/kg per day) is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents (strong recommendation; high quality evidence). The transition from AmB to fluconazole is recommended after 5-7 days in patients whose fluconazol-sensitive isolates are clinically stable and for whom cultures repeated in antifungal therapy are negative (strong recommendation; high-quality evidence). AmB lipid preparation (3-5 mg/kg per day) (strong recommendation; low-quality evidence) is recommended in patients with suspected azol and echinocandin-resistant Candida infection. Voriconazole 400 mg (6 mg/kg) twice a day in 2 doses, followed by 200 mg (3 mg/ kg) twice a day is effective for candidemia, but offers few benefits over fluconazole as an initial therapy (strong recommendation; moderate-grade evidence). Voriconazole recommended as step-down oral therapy in c. krusei (strong recommendation; low-quality evidence) due to selected candidiaemia cases. All non-neutropenia patients with candidemia should conduct dilated ophthalmic examinations within the first week of diagnosis, preferably by ophthalmologist (strong recommendation; low-quality evidence). Blood formations should be carried out every day or every other day to determine the date of deletion of candidemia (strong recommendation; low-quality evidence). Recommended duration of therapy for candidemia without obvious post-2 weeks of documented clearance of Candida species into the bloodstream, and resolution of symptoms attributed to candidemia (strong recommendation; moderate-quality evidence). Summary of evidence Ii. Should midvenous catheters be removed in nonneutropenic patients with Candidemia? Recommendation Central venous catheters (CVCs) during candidemia should be removed as soon as possible if the source is classified as CVC and the catheter can be safely removed; this decision should be taken individually for each patient (strong recommendation; moderate quality evidence). Summary of evidenceThe Central Venous Catheters and other intravascular devices are important risk factors for the development and survival of candidiaemia in non-neutropenic patients [5, 7-9, 184]. CVC is present in at least 70% of non-neutropenia patients at the time of acquisition of diagnostic blood culture [5, 7-9, 170, 184-187]. The relationship between candidemia and CVCs was assumed on the basis of observation, clinical experience and understanding of the role of biofilm in the formation of bloodstream infections [188, 189]. This candidemia in non-neutropenic patients is often due to contaminated CvC undeniable, but there remains debate as to how best to distinguish catheter-related candidemia from one that is linked to another source, such as the gastrointestinal tract. No prospective clinical studies have been conducted to investigate CVC treatment as the primary measurement associated with the results. In addition, a number of retrospective analyses have drawn very different conclusions on the need and timing of CVC removal in the candidatic patient [19, 190-193]. Thus, the debate continues, with some groups arguing for a strictly individualised approach by individual patients [190] and others in favour of an approach that removes CVCs in all non-neutropenic candidiacs for whom this is safe and feasible [19]. No prospective studies showed a survival benefit for early CVC removal in candidemia patients, but most studies showed a tendency towards shorter candidemia and/or better outcomes [14, 21-23, 27, 28, 168, 192-200]. A recent combined analysis of the 7 candidia studies observed a survival benefit among those who had at some point experienced the removal of CVC from the candidemia [19]. The survival benefit applied to patients at all levels of severity of disease is determined by APACHE II scores. Members of the panel of experts strongly believe that CCC should be removed if this can be done safely, if candidiaemia is documented in a non-neutropenic patient. It goes without saying that all patients with candidemia should be treated separately for cvc removal or preservation, but all in all, most of the data support an approach that leads to the early removal of non-neutropenia patients, for whom the catheter is likely to be a source of infection. The role of the gastrointestinal tract in neutropenic patients is evident as a source of disseminated candidiasis from autopsy studies, but it is difficult for a particular patient to determine the relative contribution of the gastrointestinal tract and CVC as the primary source of candidemia [195, 201]. The exception is candidemia due to c. parapsilosis, which is very often associated with CVCs [188, 189, 200, 202]. A recent retrospective analysis, which mainly included non-nenetropenic patients, highlighted the effect of early CVC removal, especially on the clinical outcome among patients with C. parapsilosis bloodstream infection [176]. III. What is the treatment of Candidemia in neutropenic patients? Recommendations Echinocandin (caspofungin: 70 mg, then 50 mg per day; micafungin: 100 mg per day; anidulafungin: 200 mg, then 100 mg daily loading) is recommended as an initial therapy (strong recommendation; moderate-quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, is an effective but less attractive alternative because of its potential toxicity (strong recommendation; moderate quality evidence). Fluconazole, the load dose of 800 mg (12 mg/kg), followed by 400 mg (6 mg/kg) per day, is an alternative to patients not in critical condition and has not previously had exposure to azol (poor recommendation; low-quality evidence). Fluconazole, 400 mg (6 mg/kg) per day, can be used for step-down therapy during persistent neutropenia in patients with clinically stable, sensitive isolates and documented bloodstream clearance treatment (poor recommendation; low-quality evidence). Voriconazole, 400 mg (6 mg/kg) twice a day in 2 doses, followed by 200-300 mg (3-4 mg/ kg) twice a day, can be used in situations where additional mold coverage is desirable (poor recommendation; poor quality evidence). Voriconazol can also be used during neutropenia in clinically stable patients who have documented clearance of the bloodstream and isolates sensitive to voriconazole (poor recommendation; low-quality evidence). Infections caused by c. krusei, echinocandin, lipid preparation AmB, or voriconazol are recommended (strong recommendation; low quality evidence). The recommended minimum duration for candidia without metastatic complications is 2 weeks after the documented clearance of Candida from the bloodstream, provided that neutropenia and candidaemia (strong recommendation; low-quality evidence). Ophthalmic records of choroidal and vitreal infection are minimal until recovery from neutropenia; therefore, in the first week after recovery from neutropenia (strong recommendation; low-quality evidence), dilated funduscopical studies should be performed. In a neutropenic patient, sources of candidiasis differ from CVC (eg, gastrointestinal tract) dominate. Removal of the catheter should be considered in a specific variety (strong recommendation; low-quality evidence). Granulocyte colony-stimulating factor (G-CSF)-mobilized granulocyte transfusions can be considered in the case of persistent candidemia expected with prolonged neutropenia (poor recommendation; low-quality evidence). Evidence Summary candidemia that develops in neutropenic patients with a life-threatening infection associated with acute dissemal candidiasis, sepsis-like syndrome, multiorgan failure, and death. The results are particularly poor for people with prolonged neutropenia, such as those developing after induction therapy for haematological malignant tumours [190, 203, 204]. Candidemia associated with C. tropicalis is associated with particularly poor results from neutropenic hosts. Chronic dissecting candidiasis (hepatosplenic candidiasis) may follow as a complication of candidemia in neutropenic patients, especially if patients with gastrointestinal mucosal inflammation do not receive antifungal prophylaxis. In neutropenic patients, controlled, controlled trials of candidia have not been performed in accordance with the treatment of candidia. The data were largely derived from one-arm studies, small subgroups of randomised controlled trials, which mostly involved non-neutropenic patients, and from the overall results of randomised studies [205, 206]. Historically, candidiatic neutropenic patients have been treated with AmB preparation. The availability of voriconazole and echinocandins has led to greater use of these agents, but without compelling clinical data. The widespread use of fluconazole for prophylaxis for the prevention of invasive candidiasis in neutropenic patients and the lack of meaningful prospective data have reduced the therapeutic role of this drug in patients, except for use as maintenance treatment or step-down therapy after body species and sensitivities in clinically stable patients [207]. The number of neutropenic patients in candidia treatment studies is small. In these studies, 50% vs. 40% of those receiving AmB deoxykolate [25], 68% vs. 61% of micafungin recipients were successfully treated with 61% of liposomal AmB recipients [26]. In a controlled trial randomised anidulafungin vs fluconazol, too few neutropenic patients with candidemia were ed to generate meaningful efficacy data [27]. In two retrospective studies, the outcome of primary treatment for neutropenic patients was reported in 64% of patients receiving AmB deoxykolate, 64% of patients receiving fluconazole and 68% of patients receiving caspofungin [29,208]. Further insights can be obtained from data from studies from empirical antifungal treatment, which also involved febrile patients with

neutropenia who had candidemia at the start of the study. In these studies, baseline candidemia was treated with AmB deoxycolate in 73%, compared with 82% with liposomal AmB [209] and 67% with caspofungin, compared with 50% of those treated with liposomal AmB [210]. Data from a large randomised study also suggest that voriconazole is a reasonable choice for patients with feverish neutropenia and suspected invasive candidiasis who need additional mold coverage [211]. A systematic review has been carried out to analyse the available data in treatment studies and empirical therapy studies in neutropenic patients [205]. This included 17 studies randomised 342 neutropenic patients with documented invasive candidiasis. Merging results is a preference for the use of nonpolienes for amB-containing comparators. Another overall analysis summarising the results of the treatment of micafungin or comparative (liposome AmB or caspofungin) with candidaemia in the setting of malignant tumour-related neutropenia from 2 randomised studies showed a success rate of between 53% and 85%, but there was no significant difference between treatment groups [206]. Based on these limited data, the success rate of candidiatic paratanus antifungal treatment in neutropenia does not appear to be significantly different from that reported in large randomised studies in non-neutropenic patients. However, the conclusions may be limited by the significant enrolment bias of selected patients. Although these data do not suggest less favorable results associated with fluconazole and voriconazole, many experts prefer lipid formulation AmB or echinocandin, which are fungicidal, as first-line agents. Similar to the approach in non-neutroptropic patients, the recommended duration of candidia in neutropenic patients is 14 days after the cessation of the bloodstream of candida species, provided that neutropenia has been restored. If neutropenia is prolonged, the antifungal drug should be continued until implantation. This recommendation is based on limited data from prospective randomised studies and has been associated with some complications and relapses [209, 210]. Treatment of intravascular catheters in neutropenic patients with candidiasis is less simple than in their non-neutropenic counterparts. Distinguishing between gut-related vascular-related candidemia can be difficult in these patients [201]. To remove the catheter data are less convincing and catheter removal often causes significant intravenous access problems. Analysis of 842 patients no significant clinical benefit of catheter removal has been demonstrated in phase 2 treatment studies in multi-variable analyses that have been adjusted to other measures of prognostic importance [190]. The panel of experts recommends that the removal of the catheter be considered individually, taking into account feasibility and the risk of removal. An extremely important factor influencing the outcome of candidiaemia in neutropenic patients is the restoration of neutrophils during therapy. In multiple cohort studies of cancer patients with candidemia and in the pooled analysis of randomised studies, persistent neutropenia was more likely to fail treatment [190, 203, 204, 212]. This has led to improvements in strategies for harvesting granulocytes from donors (including Community volunteers) using g-CSF mobilisation, which have been shown to be safe and feasible [213]. Analysis of subgroups of people in Phase 1/2 granulocyte infusion studies, retrospective observations and small cohort studies suggests that granulocyte transfusion mobilised by G-CSF may be beneficial in persistent candidia and prolonged neutropenia [213-215]. In a randomised controlled study, granulocyte infusions had little toxicity, but a small number of patients in the subgroup limited the conclusions of efficacy [216]. The panel recommends considering granulocyte infusions in certain situations when this technology is feasible. IV. What is the treatment of chronic disseminated (hepatosplenic) candidiasis? Recommendations For initial therapy with lipid preparation AmB, 3-5 mg/kg daily or echinocandin (micafungin: 100 mg per day; caspofungin: 70 mg loading dose, then 50 mg daily; or anidulafungin: 200 mg loading dose, then 100 mg daily), recommended for several weeks, followed by oral fluconazole, 400 mg (6 mg/ kg) per day, in patients unlikely to have fluconazole-resistant isolate (strong recommendation; low-quality evidence). Therapy should be continued until the lesions are dissolved during repeated imaging, which is usually several months. Premature discontinuation of antifungal treatment can lead to relapse (strong recommendation; low-quality evidence). If chemotherapy or haematopoietic cell transplantation is required, it should not be delayed due to the presence of chronic disseminated candidiasis and antifungal therapy should be continued throughout the period of high risk for the prevention of relapse (strong recommendation; low-quality evidence). In patients who have desensitating persistent fever, short-term (1-2 weeks) treatment with nonsteroidal anti-inflammatory drugs or corticosteroids may be considered (poor recommendation; low-quality evidence). Summary of evidence Chronic disseminated candidiasis is a rare syndrome seen almost entirely in patients who have hematological malignancy and who have just recovered from neutropenia Candida albicans a leggyakrabban izolált, de C. tropicalis, C. glabrata, C. krusei, krusei, other Candida species are also affected. Fever, right upper quadrant discomfort, nausea, and an increase in liver icing occur after the return of neutrophils and persist for months, unless treatment is started. Contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT), and sometimes ultrasound have all proved useful for diagnosis and follow-up [217, 218, 220, 221]. Biopsy lesions may reveal budding yeasts and hyphae, but organisms are not seen in biopsy specimens and often do not grow in culture, leading some to suggest that chronic disseminated candidiasis represents immune reconstitution syndrome [219]. The approach to the treatment of chronic disesmal candidiasis is based on anecdotal case reports and open series. Early experience with amb discouraged; one third of patients died of an active infection within 3 months and total mortality was 74% [222]. With the use of newer antifungal agents, mortality overall decreased to 21% and is strongly linked to a decline in leukemia [223]. AmB lipid formulations have been shown to be more effective, perhaps related to improved tissue concentration [217, 218, 224, 225]. Fluconazole has been shown to be effective on its own or after AmB induction [226, 227]. Patients are increasingly receiving fluconazol prophylaxis and thus at increased risk of developing infection with a fluconazol-resistant organism. In this population, broader-spectrum azol or echinocandin is more appropriate therapy. Only a few reports take into account the experience of voriconazole or posacanazole for this condition, but echinocandins are increasingly used to treat infection [219, 223, 228-231]. Antifungal therapy should be used until all lesions are radiologically eliminated to prevent relapse. Mri or PET-CT appears to be the most sensitive method of monitoring, but it is expensive [220, 221]; CT with normal contrast is less expensive and suitable for tracking. Further chemotherapy and ha ha ha haemia cell transplantation should be continued if clinically appropriate and not delayed due to candidiasis. However, in order to prevent relapse of infection, antifungal treatment should be continued during immunosuppression [219, 223, 228-231]. There is evidence that this syndrome may be a form of immune reconstitution and that corticosteroids or anti-inflammatory drugs may play a role in selected patients. A number of investigators reported rapid defervescence and improvement in liver-based tests when corticosteroids were given together with antifungal drugs [219, 223, 232, 233]. The dose of corticosteroids is usually 0.5-1 mg/kg per day of oral prednisot. The duration of steroid treatment, although very variable, in most cases has been several weeks since the tapered dose [232, 233]. However, the role of corticosteroids in this disease it's always unclear. Clear. What is the role of empirical treatment in suspected invasive candidiasis nonneutropenic patients in the intensive care unit? Recommendations Empirical antifungal therapy should be considered in patients with critically ill invasive candidiasis risk factors and no other known cause of fever is necessary and should be based on clinical assessment of risk factors, replacement markers for invasive candidiasis and/or breeding data from non-sterile sites (strong recommendation; moderate quality evidence). Empirical antifungal therapy should be started as soon as possible in patients with the above risk factors and who have clinical signs of septic shock (strong recommendation; moderate quality evidence). Preferred empirical therapy for suspected candidiasis nonneutropenic patients in the intensive care unit (ICU) is an echinocandin (caspofungin: load dose 70 mg, then 50 mg per day; micafungin: 100 mg per day; anidulafungin: loading dose 200 mg, then 100 mg daily) (strong recommendation; moderate quality evidence). Fluconazole, a load dose of 800 mg (12 mg/kg), followed by 400 mg (6 mg/kg) per day is an acceptable alternative for patients who have not had fresh azol exposure and have not been colonised with azol-resistant Candida species (strong recommendation; moderate-quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, is an alternative if there is intolerance to other antifungal agents (strong recommendation; low-quality evidence). Recommended duration of empirical therapy for suspected invasive candidiasis in patients who improve by 2 weeks, is the same as treatment documented candidemia (poor recommendation; low-quality evidence). Patients who do not have a clinical response to empirical antifungal treatment at 4-5 days of age and who have no subsequent evidence of invasive candidiasis after initiation of empirical therapy or who have a negative non-culture-based diagnostic study with a high negative predictive value should consider discontinuing antifungal therapy (strong recommendation; low-quality evidence). Evidence Summary Candida species are a growing cause of invasive infection in non-neutropenic patients in the intensive care unit; between half and two thirds of all episodes of candidiaemia occur in intensive care [5, 14, 167, 170, 234]. Candida bloodstream infections are associated with increased ICU and hospital stay [129, 235]. Most estimates of invasive candidiasis mortality in this setting are 30%-40% [167,170]. In patients who have had septic shock due to candida species and who do not have adequate source control or antifungal therapy started within 24 hours, mortality is close to 100% [14]. Immediate initiation of appropriate antifungal treatment was associated with a 50% reduction in mortality [14, 17, 18, 236]. Rapid and appropriate antifungal therapy is often delayed due to the relative insensitivity of blood cultures, due to the possibility of negative blood cultures. candidiasis of the abdomen, as well as lack of specific clinical signs and symptoms. Strategies for insanting empirical antifungal therapy include evaluating risk factors and using replacement markers. Optimal use of risk factors and colonisation status derived from clinical scoring systems, as well as interpretation of non-culture-based diagnostic studies to identify patients with invasive candidiasis at the initiation of early empirical antifungal therapy, have been the subject of a number of studies. Retrospective and one-center studies have produced conflicting results, depending on individual patient populations. Well-planned prospective clinical trials in this area have been difficult to carry out and many unanswered questions remain. Risk factors for the development of invasive candidiasis include Candida colonization, severity of disease, exposure to broad-spectrum antibiotics, recent major surgery, especially abdominal surgery, necrotizing pancreatic care, dialysis, parenteral nutrition, corticosteroids, and the use of CVCs [237, 238]. Empirical therapy based solely on colonisation with Candida species does not appear to be appropriate [16, 239]. Forward-looking studies evaluating the extent of Candida's convakolisation based on scores or indices have not shown that they change management and are labour-intensive and costly [234]. Several studies have examined forecasting models to identify patients at greatest risk. These studies are characterised by high specificity but low sensitivity, so many patients with candidiasis are absent [240-242]. In a subset of postoperative patients, especially patients with recurrent gastrointestinal perforation, anastomotic leakage or acute necrotizing pancreatic bypass, the risk of candidiasis may be uniquely high [238, 240, 243, 244]. The combination of the most important factors in each patient is unknown. Substitute markers evaluated in the ICU setting include β-D-glucan, manmanan antimannan antibodies and PCR tests. β-D-glucan appears to be more sensitive than Candida's colonisation scores or indices, but appears to have a low positive predictive value [245-248]. False positive results are a problem, as noted in the Background section. The optimal timing and number of samples are unknown. In a recent prophylaxis study of patients in the high-risk Intensive Care Unit, β-D-glucan study was conducted twice a week identified 87% of patients with proven candidiasis [249]. Small studies based on β-D-glucan study suggest that a high negative predictive value of the study may be useful in excluding invasive candidiasis in intensive care [151, 248, 250-252]. The combinedmannan-antimannan test has varying sensitivity and specificity [142, 253]. It seems that real-time PCR has a sensitivity β-D-glucan for the diagnosis of candidemia, but may be more susceptible to the diagnosis of other forms of invasive candidiasis [132]. Magnetic biosensor technology tests for the rapid detection of Candida species from whole blood samples biosystems) are also promising [163]. Recommendations for the clinical use of these studies are challenging without reliable data in the vulnerable intensive care unit. Limited clinical studies have evaluated the effectiveness of empirical strategies. Retrospective studies indicate a higher survival potential when empirical antifungal therapy is given to high-risk patients [254]. Prospective clinical studies on empirical antifungal therapy in the intensive care unit are difficult to carry out and have produced conflicting results. Some older studies, including studies in individual patient groups, such as those with previous gastrointestinal surgery or intestinal perforation, showed potential benefits [255, 256]. In a randomised clinical trial in an intensive care unit at risk of invasive candidiasis and an intensive care unit with unexplained fever, empirical fluconazole (800 mg daily for 14 days) did not have better results compared to placebo [257]. A recent study comparing caspofungin to placebo among ICU patients with signs of infection, Candida colonization, and clinical risk factors for invasive candidiasis stopped prematurely due to poor patient demargation, confirming the difficulty of conducting these studies [249]. The widespread use of antifungal agents should be balanced with costs, risk of toxicity and the development of resistance. None of the existing clinical trials was adequately mandated to assess the risk of developing azol or echinocandin resistance. Empirical antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever. Preference should be given to echinocandin in hemodynamically unstable patients, patients previously exposed to azol, as well as in patients colonized with azol-resistant Candida species. Fluconazole may also be considered in haemodynamically stable patients who have settled with azol-sensitive Candida species or who have not previously been exposed to azazol. There are no data showing adequate duration of empirical antifungal therapy in patients who have responded clinically to treatment, but it is logical that this does not differ from the treatment of documented candidemia. Conversely, therapy can be stopped after a few days in the absence of a clinical response if cultures and replacement markers are negative. VI. Should prophylaxis be used to prevent invasive candidiasis in the intensive care unit setting? Recommendations Fluconazole, 800 mg (12 mg/kg) load dose, then 400 mg (6 mg/kg) per day can be used at high risk, high risk, high proportion (>5%) (poor recommendation; moderate-quality evidence). Another option is to take an echinocandin (caspofungin: 70 mg loading dose, then 50 mg daily; anidulafungin: 200 loading dose, then 100 mg per day; or micafungin: 100 mg per day) (poor recommendation; low quality evidence). Daily bathing of patients in the intensive care unit with chlorhexidine, which has been shown to reduce blood flow including candidemia, could be considered (weak recommendation; moderate-quality evidence). Evidence Summary of appropriate therapy for candidiasis appears to have a significant impact on the outcome of patients with infection [14, 17, 18]. However, insensitivity and significant delays in breeding techniques, as well as the limitations of rapid diagnostic tests, remain this common cause of bloodstream infection among patients in intensive care [258, 259]. A safe and effective prophylactic strategy for the prevention of candidemia in high-risk patients can be of great benefit [260]. The approach to prophylaxis was either widespread, in which all patients in the intensive care unit are treated [261, 262], or selective, in which only specific high-risk groups of patients are targeted for prophylaxis [249, 263, 264]. In IMUs with a very high rate of invasive candidiasis, antifungal prophylaxis may be justified in selected patients at highest risk in excess of the expected rate of <5%[260]. In two randomised placebo-controlled studies, the incidence of invasive candidiasis decreased in a single unit or in a single hospital when fluconazole prophylaxis was widely used in intensive care; one study targeted all patients in the surgical intensive care unit [262] and all patients receiving mechanical ventilation in the other [261]. In both studies, Candida urinary tract infections, as well as invasive candidiasis and candidemia, were taken as endpoints. In a blind placebo-controlled study with a small number of patients, fluconazole prophylaxis was shown to reduce intraabdominal infections of Candida in the surgical intensive care unit [263]. A non-comparative open-study using caspofungin prophylaxis in some similar high-risk surgical patients was also beneficial [264]. In a recent multicentre placebo-controlled, blind clinical trial of caspofungin prophylaxis targeting only icu patients who met the specific criteria for a high risk of invasive candidiasis showed a tendency to reduce invasive candidiasis, but limited sample size [249]. A number of meta-analyses evaluated the issue of fluconazol prophylaxis in intensive care patients [265-268]. Not surprisingly, there were methodological differences between the studies and also differences between study populations. All 4 meta-analyses showed that fluconazole prophylaxis was associated with a decrease in invasive candidiasis, but only 2 showed a decrease in candidemia [267,268]. It is important that only one analysis showed a decrease in mortality caused by invasive candidiasis [268]. None of the meta-analyses evaluated the adverse effects of antifungal agents, the development of resistance to fluconazol, or the significant ecological shift of Candida species. topics of great importance in the context of intensive care. The Cochrane analysis confirmed the importance of focusing prophylactic efforts on high-risk patients, invasive candidiasis in the intensive care unit varied from 9 to 188 in high-risk patients [269]. There is little data on candidiasis risk factors in paediatric intensive care unit (PICU) patients. A population-based case-control study in a large tertiary paediatric centre found the incidence of candidemia at 3.5 per 1,000 PICU admissions [270]. The presence of CVC, the diagnosis of a malignant tumor and the arrival of vankomycin or antianaerobic antimicrobials for >3 days are independently associated with candidemia. Children who had ≥3 of these risk factors in different combinations had a predicted likelihood of developing candidemia between 10% and 46%. The data accumulate on the use of skin decolonization antiseptic agents in the intensive care unit to reduce bloodstream infections, including those caused by Candida species [271-274]. A number of multicentre randomized clinical trials have shown that daily bathing in intensive care patients with chlorhexidine reduces the incidence of both catheter-related and non-catheter-related hospital-acquired bloodstream infections [271-273]. These studies were primarily aimed at assessing the effect on multi-resistant bacterial infections and provided little data on Candida infections. However, at least one of these studies found a significant reduction in catheter-related Candida bloodstream infections [272]. The meta-analysis of the effects of daily chlorhexidine bathing included 10 intensive care studies, only one of which was a randomised controlled trial. The conclusion was that chlorhexidine bathing reduced the incidence of bloodstream infections, including catheter-related bacterial infections [274]. While it has not been proven to prevent candidemia, there is little risk of chlorhexidine in intensive care patients, and this practice may prove useful. VII. What is the treatment of neonatal candidiasis, including central nervous system infection? What is the treatment of invasive candidiasis and candidiaemia? Recommendations for AmB deoxycolate, 1 mg/kg per day, recommended for neonates distributed candidiasis (strong recommendation; moderate quality evidence). Fluconazole, 12 mg/kg intravenous or daily oral, is a reasonable alternative in patients who have not received fluconazole prophylaxis (strong recommendation; moderate quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, is an alternative, but should be used with caution, especially in the presence of urinary tract affected (poor recommendation; low-quality evidence). Echinocandins should be used with caution and should generally be limited to rescue therapy or situations where resistance or toxicity precludes the use of AmB deoxyzole or fluconazole (poor recommendation; low-quality evidence). Lumbar surgery and dilated retinal examination are recommended in from blood and/or urine to candida species with positive cultures (strong recommendation; low quality Computed tomography or ultrasonic imaging of the urogenital tract, liver and spleen should be carried out if the blood cultures are persistently positive for Candida species (strong recommendation; low-quality evidence). Removal of CVC is highly recommended (strong recommendation; moderate quality evidence). The recommended duration of treatment of candidemia without obvious post-infectious complications is 2 weeks after documented excretion of Candida species from the bloodstream and resolution of symptoms attributable to candidemia (strong recommendation; low-quality evidence). Evidence summary What is the treatment of CNS infections neonate? Recommendations for initial treatment, AmB deoxycolate, 1 mg/kg intravenous daily, recommended (strong recommendation; low quality evidence). An alternative treatment is liposomal AmB, 5 mg/kg per day (strong recommendation; low quality evidence). This addition of flucytosin, 25 mg/kg 4 times a day, is considered residual therapy in patients who have not responded clinically to initial AmB treatment, but side effects are common (poor recommendation; low-quality evidence). After the discharge treatment, the patient responded to initial treatment, fluconazole, 12 mg/kg per day, recommended isolates that are sensitive to fluconazole (strong recommendation; low-quality evidence). Therapy should continue until all signs, symptoms and cerebrospinal fluid (CSF) and radiological disorders, if present, are eliminated (strong recommendation; low-quality evidence). Infected central nervous system (CNS) devices, including ventriculostomy channels and stents, should be removed, if at all possible (strong recommendation; low-quality evidence). Summary of evidence Limited data are available to guide the treatment of CNS Candida infections in newborns. All AmB preparations, including lipid preparations, penetrate cns and have a fungicide effect in cns [44]. AmB identified deoxysolate and liposomal AmB as higher antifungal efficacy in the rabbit model of Candida meningoencephalitis than in other preparations [44]. The clinician should weigh the pros and cons of using liposomal AmB for good CSF penetration, but poor urine levels vs. using AmB deoxycholate have less good CSF levels, but better urine levels. The addition of flucytosine to neonates with cns candidiasis is uncertain. In the largest prospective study to assess the treatment results of cns candidiasis in neonates, the median time to clarify CSF was longer for those who received flucytosine and AmB deoxycolate (17.5 days; 6 infants), compared with those who received only AmB deoxicolate (6 days; 18 infants) [279]. In addition, flucytosine is poorly tolerated and gastrointestinal side effects can hinder oral feeding of new goats. In general, flucytosine is only used in neonates who have not responded exclusively to AmB. Echinocandins underpinning the use of the however, a number of key issues require further clarification. The optimal dose of echinocandins in new consumers remains uncertain [109, 284, 293-297]. Furthermore, there are concerns about the penetration of echinocandins into CSF. Echinocandins appear to penetrate brain tissue, but not CSF, and to achieve concentrations in the brain have been shown to be effective in animal models when dosages higher than those recommended in humans have been used [298, 299]. Limited clinical data suggest that echinocandins may be effective in treating CNS infections in nenotok, but are not appropriate to recommend their use at this time [293]. What are the recommendations for prophylaxis in the neonatal intensive care unit setup? Recommendations High percentage of nurseries (>10%) invasive candidiasis, intravenous or oral fluconazole prophylaxis, 3-6 mg/kg twice a week for 6 weeks, newborns with birth weight <1000 g recommended (strong recommendation; high quality evidence). Oral nystatin, 100,000 units per day 3 times for 6 weeks, is an alternative to fluconazole with neonazole birth weight <1500 g in situations where availability or resistance excludes fluconazole (poor recommendation; moderate quality evidence). Oral bovine lactoferrin (100 mg per day) may be effective for neonate < 1500 g, but is not currently available in U.S. hospitals (poor recommendation; moderate quality evidence). Summary of evidence A number of studies examining the prophylaxis of fluconazole to prevent invasive candidiasis of neonates have consistently demonstrated efficacy and possibly reduced mortality [300-310]. Fluconazole, 3 mg/kg or 6 mg/kg twice a week, significantly reduced the rate of invasive candidiasis in preterm neonates weight < 1000 g in nurseries with a very high incidence of candida infections [300,302]. The 2007 Cochrane study of fluconazole prophylaxis demonstrated efficacy, with a typical relative risk of 0, 23 and 9 treatment numbers. The number required for treatment differed significantly depending on the incidence of invasive candidiasis in a specific intensive care unit. The majority of studies demonstrated the safety of fluconazole prophylaxis and the absence of resistance. Enteral or oral nystatin has been shown to effectively reduce invasive candidiasis in premature infants [303, 311-313]. In one study, nystatin prophylaxis was also associated with a decrease in total mortity [313]. However, there remains little data on nystatin prophylaxis in infants <750 grams (the group at greatest risk), and nystatin may not always be administered if there is an ileus, gastrointestinal disease, feeding intolerance, or hemodynamic instability. These clinical situations are very common in premature infants of low gestational age and are limited as a strategy to prevent the widespread use of nystatin prophylaxis. A a mammalian milky glycoprotein, which is involved in congenital immunity. A One a 24 órán át nem <1500 g,= the= incidence= of= late-onset= sepsis= was= significantly= lower= in= the= lactoferrin= group= than= in= the= placebo= group= [314].= a= secondary= analysis= of= the= clinical= trial= showed= that= lactoferrin= also= reduced= the= incidence= of= invasive= fungal= infections= compared= with= placebo= [314].= further= confirmation= of= the= efficacy= and= safety= of= oral= bovine= lactoferrin= for= the= prevention= of= invasive= candidiasis= is= needed,= especially= in= infants=></1500> <750 g,= because= there= were= only= a= few= neonates= in= this= category= in= this= trial.= viii.= what= is= the= treatment= for= intra-abdominal= candidiasis?= recommendations= empiric= antifungal= therapy= should= be= considered= for= patients= with= clinical= evidence= of= intra-abdominal= infection= and= significant= risk= factors= for= candidiasis,= including= recent= abdominal= surgery ,= anastomotic= leaks,= or= necrotizing= pancreatitis= (strong= recommendation;= moderate-quality= evidence).= treatment= of= intra-abdominal= candidiasis= should= include= source= control,= with= appropriate= drainage= and/or= debridement= (strong= recommendation;= moderate-quality= evidence).= the= choice= of= antifungal= therapy= is= the= same= as= for= the= treatment= of= candidemia= or= empiric= therapy= for= nonneutropenic= patients= in= the= icu= (see= sections= i= and= v)= (strong= recommendation;= moderate-quality= evidence).= the= duration= of= therapy= should= be= determined= by= adequacy= of= source= control= and= clinical= response= (strong= recommendation;= low-quality= evidence).= evidence= summary= intra-abdominal= candidiasis= in= patients= who= have= had= recent= abdominal= surgery= or= intra-abdominal= events= refers= to= a= heterogeneous= group= of= infections= that= includes= peritonitis,= abdominal= abscess,= and= purulent= or= necrotic= infection= at= sites= of= gastrointestinal= perforation= or= anastomotic= leak.= up= to= 40%= of= patients= with= secondary= or= tertiary= peritonitis ,= as= defined= by= a= multinational= consensus= panel,= may= develop= intra-abdominal= candidiasis= with= a= high= mortality= rate= [243,= 244,= 315,= 316].= a= subset= of= postsurgical= patients,= particularly= those= with= recurrent= gastroduodenal= perforation,= anastomotic= leaks,= or= acute= necrotizing= pancreatitis,= are= at= uniquely= high= risk= for= invasive= candidiasis= [243,= 244,= 263,= 316–320].= in= other= settings,= such= as= perforated= appendicitis,= invasive= candidiasis= appears= to= be= a= rare= complication= [316,= 319].= infections= are= often= polymicrobial,= with= yeast= noted= in= as= high= as= 20%= of= all= cases= and= 40%= in= patients= with= a= recent= gastroduodenal= perforation= [319,= 320].= diagnosis= is= hampered= by= the= lack= of= specific= clinical= signs= and= symptoms.= blood= cultures= are= often= negative= [321].= a= laboratory= report= of= yeast= isolated= from= an= abdominal= specimen= be= evaluated= to= distinguish= between= contamination,= colonization,= and= invasive= infection.= swabs= of= superficial= wounds= and= specimens= taken= from= intra-abdominal= catheters= that= have= been= in= place= for=>szolgálnak hasznos információkkal, ezért nem szabad elvégezni. Ezzel szemben a normálisan steril hasüregi</750> hasüregi</750> (surgical samples and/or drains placed within 24 hours) in patients with clinical evidence of infection should be considered as suggestive of abdominal candidiasis. The role of surrogate markers and Candida risk scores in this setting was not created. There is limited data β the use of β-D-glucan in post-information patients with suspected abdominal candidiasis. In one study, β-D-glucan had a 72% positive predictive value and 80% negative predictive value to distinguish colonization from abdominal invasive candidiasis and performed better than Candida colonization scores or indices [143]. Clinical evidence for the use of antifungal therapy is limited in patients with suspected abdominal invasive candidiasis. Most studies are small, unverified, one-center, or conducted in certain populations. Patients whose Candida species have been isolated from sterile abdominal cultures or drains within 24 hours and who have evidence of clinical infection should be treated for abdominal candidiasis. Patients who have had gastroduodenal perforation, anastomotic leakage, necrotizing pancreatitis or other abdominal events without isolation of Candida species and who perform poorly despite the treatment of bacterial infections may receive empirical antifungal therapy. Many meta-analyses of antifungal prophylaxis in patients in high-risk surgical intensive care have produced conflicting results [265-268]. Resource control with adequate drainage and/or cleaning is an important part of the therapy of candidiasis in the abdomen [14]. The excretion of the antifungal agent should be guided by knowledge of isolated Candida species and local epidemiology, including antifungal sensitivity patterns. The duration of antifungal treatment should be guided by clinical response and the adequacy of radiation control. IX. Does the respiratory isolation of Candida species require antifungal therapy? Recommendation Candida growth from respiratory secretions usually indicates colonization and rarely requires antifungal treatment (strong recommendation; moderate quality evidence). Summary of evidence Separation of Candida species from the airways often meets in patients in intensive care and intubated or with chronic tracheostomy. This almost always reflects the colonization of the respiration of the respiratory tract and not the infection. Candida pneumonia and lung abscess are very rare [322, 323]. Only rarely is aspiration of oropharyngeal substance primary Candida pneumonia or abscess documented [324, 325]. Pneumonia due to Candida species is usually limited to severely immunocompromising patients who have experienced infection after hematogen has spread to the lungs. Chest CT usually shows multiple lung nodes. Isolation of Candida species from respiratory samples in patients who are severely immunosuppressant, invasive candidiasis. Although the diagnosis of Candida pneumonia is supported by the isolation of the body from the bronchoalveolar lavage (BAL) sample, a definite diagnosis requires histopathological evidence of invasive disease. Several prospective and retrospective autopsy studies have consistently demonstrated the weak predictive value of Candida's growth from respiratory secretions, including BAL fluid [326-328]. In one prospective study, none of the 77 patients who died in intensive care showed candida pneumonia and a positive culture for THE LEFT or sputum Candida species [328]. Candida pneumonia is a rarity, an extremely common find of Candida in respiratory secretions, and due to the lack of specificity of this finding [329-331], the decision to initiate antifungal treatment should not be taken solely on the basis of the results of respiratory culture. Recent observations suggest that colonisation with candida species is linked to the development of bacterial colonisation and pneumonia [332-336]. Candida respiratory colonisation was also associated with worse clinical outcomes and higher mortality in these studies. However, it is unclear if Candida's respiratory colonization has a causal relationship with worse outcomes or is simply a marker of the severity of the disease. X. What is the treatment for Candida invasive infections, including endocarditis and infections implantable in heart devices? What is the treatment for Candida myocarditic thing? Recommendations for native valve endocarditis, lipid preparation AmB, 3-5 mg/kg daily, with or without flucytosine, 25 mg/kg 4 times daily, OR high doses of echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily) recommended initial therapy (strong recommendation; low quality evidence). Step-down therapy with fluconazol, 400-800 mg (6-12 mg/kg) per day, is recommended for patients who are susceptible to Candida isolates, demonstrated clinical stability and cleared Candida into the bloodstream (strong recommendation; low quality evidence). Oral voriconazole, 200-300 mg (3-4 mg/ kg) twice a day, or posaconazole tablets, 300 mg per day, can be used as step-down therapy isolates that are susceptible to those agents but are not sensitive to fluconazole (poor recommendation; very poor quality evidence). Valve replacement is recommended; treatment should be continued for at least 6 weeks after surgery and for a longer period of time in perivalvular abscesses and other complications (strong recommendation; low-quality evidence). In patients who can not go through valve replacement, long-term suppression of fluconazole, 400-800 mg (6-12 mg/kg) per day if the isolate is sensitive, recommended (strong recommendation; low-quality evidence). For prosthetic valve endocarditis, the same antifungal treatment recommended for native valve endocarditis is recommended (strong evidence of poor quality). Chronic suppressive antifungal treatment fluconazol, 400-800 mg (6-12 mg/ kg) per day, is recommended to prevent recurrence (strong recommendation; low-quality evidence). Summary of evidence The incidence of Candida endocarditis increased as candida infections increased overall [337]. Endocarditis should be suspected if blood cultures are persistently positive, if the patient has candidemia with persistent fever despite proper treatment, or if a new heart murmur, heart failure, or embolism phenomena occur in the setting of candidemia [338]. Most cases occur after heart valvular surgery, but other risk factors include injectable drug use, cancer chemotherapy, prolonged presence of CVC, and previous bacterial endocarditis. Signs, symptoms and complications are usually similar to bacterial endocarditis, except for the frequent occurrence of large embolisms in larger vessels. The cases are fairly evenly distributed between the species C. albicans and non-albicancancans Candida [339]. Medical therapy for Candida endocarditis was sometimes curative [340-348], but optimal therapy for native and prosthetic valve endocarditis in adults is a combination of valve replacement and long antifungal therapy based on case reports, series of cases, cohort studies, metaanalysis and clinical experience [339, 349]. Valve repair and vegetectomy are alternatives to valve replacement. The majority of cases reported in the literature were treated with AmB deoxykolate with or without flucytosine [339, 342, 349-355]. Fluconazol monotherapy is associated with an unacceptably high relapse and mortality rate [354]. However, fluconazole is useful for step-down therapy. The AmB deoxycolate and azazols decreased activity compared to echinocandins against biofilms formed by Candida in vitro and penetrate poorly into vegetation. AmB's echinocandins and lipid preparations show a more potent activity compared to Candida biofilms [356]. A prospective, open-label clinical trial, cohort studies, and multiple case reports show a role for echinocandins in the treatment of endocarditis [228, 346, 348, 357-365]. Higher doses of echinocandins are thought to be necessary for the treatment of the endocarditis [228, 365]. Caspofungin was used as monotherapy and in combination with AmB, azoles or flucytosin in individual reports, but limited data on other echinocandins [346, 360, 361, 363, 365, 366]. Lifelong suppressive therapy of fluconazole was successfully used after basic therapy in patients with contraindication for cardiac surgery; it is also recommended to prevent a late recurrence of Candida prosthetic valve with cardiac palsy [360, 367, 368]. Since Candida endocarditis is prone to relapse months or years later, follow-up should be maintained for a few years after treatment [350, 351]. What is the treatment of infection can be implanted Tools? Recommendations pacemaker and implantable heart defibrillator infections, the whole device should be removed (strong recommendation; moderate quality evidence). Antifungal therapy is the same as recommended for native valve endocarditis (strong recommendation; low quality evidence). For infections limited to generator pockets, 4 weeks of antifungal therapy is recommended after removal of the device (strong recommendation; low-quality evidence). In the case of infections affecting the ducts, antifungal treatment of at least 6 weeks is recommended after wiring removal (strong recommendation; low-quality evidence). For ventricular assist devices that can not be removed late, antifungal treatment is the same as recommended for native valve endocarditis (strong recommendation; low-quality evidence). Chronic suppressive therapy with fluconazol, if the isolate is sensitive, as long as the device remains in place recommended (strong recommendation; low-quality evidence). Summary of evidence There are some case reports and a single retrospective review of candida pacemaker and heart defibrillator infections [369-374]. The whole device should be removed and antifungal therapy given for 4-6 weeks depending on whether the infection affects the wires outside the generator pocket [369, 371-374]. Medical treatment alone failed [370]. There are isolated case reports and a series of cases of Candida infections of ventricular aids [375-378]. The panel of experts believes that suppressive azol therapy after the entire process of initial antifungal therapy is justified. Many of these devices can not be removed, and oppression lasts a lifetime. The role of antifungal prophylaxis in preventing infection in all patients receiving assistance remains controversial [378]. What is the treatment for Candida Suppurative Thrombophlebitis? Recommendations for catheter removal and pruning and drainage or resection of the vein, if feasible, recommended (strong recommendation; low quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, OR fluconazole, 400-800 mg (6-12 mg) per day, or echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily) recommended at least 2 weeks after candidemia (if any) (strong recommendation; low quality evidence). Fluconazole 400-800 mg (6-12 mg/kg) step-down therapy per day should be considered in patients who initially responded to AmB or an echinocandin, are clinically stable and have fluconazol-sensitive isolates (strong recommendation; low-quality evidence). The dissension of the thrombus can be used as evidence to discontinue antifungal treatment if supported by clinical and breeding data (strong recommendation; low-quality evidence). Evidence summary Most of the experience in treating suppurative thrombophlebitis has been with AmB deoxycolate. Fluconazole and caspofungin were also successful in some cases [379-381], but other primary treatment for candidia, including echinocandins and voriconazol, should be effective [382]. Higher than usual doses of echinocandins should be used, similar to endocarditis therapy. Surgical exciation of the vein plays an important role in the treatment of candida thrombophlebitis of the peripheral vein. When it comes to a central vein, surgery is usually not an option. In some cases, systemic anticoagulant or thrombolytic therapy has been used as complementary therapy, but there is insufficient data to recommend their use. Thrombolytic therapy, together with antifungal therapy, was successfully used in the treatment of CVC-linked infected thrombus in patients with persistent candidemia [381]. XI. What is the treatment of Candida osteoarticular infections? What is the treatment of Candida Osteomyelitis? Recommendations Fluconazol, 400 mg (6 mg/kg) per day, For 6-12 months or echinocandin (50-70 mg of caspofungin per day, 100 mg of micafungin or 100 mg of anidulafungin per day) for at least 2 weeks, then fluconazole, 400 mg (6 mg/kg) per day, recommended for 6-12 months (strong recommendation; low quality evidence). Lipid preparation AmB, 3-5 mg/kg per day for at least 2 weeks, followed by fluconazole, 400 mg (6 mg/ kg) per day, 6-12 months is a less attractive alternative (poor recommendation; low quality evidence). Surgical debridement is recommended in some cases (strong recommendation; low-quality evidence). Summary of evidence Most patients with osteomyelitis range from subacute to chronic [383, 384]. The most common mechanism of infection is hematogenic distribution, but also the direct ino99ing and contiguous spread of infection. The involvement of 2 or more bones is common, so if a single focus of infection is identified, it is necessary to look for other affected sites. Axial skeleton, especially the spine, is the most common place for participation in adults; long bones are more commonly affected in children [228, 384-388]. Neither the clinical picture nor the results of X-ray imaging are specific to Candida infection. Candida albicans remains the dominant pathogen. However, 2 retrospective reviews in a number of cases found that non-albicans candida were an increasingly common cause of Candida osteomyelitis and mixed infections with bacteria, especially Staphylococcus aureus, were not uncommon, stressing the need for biopsy and culture [384, 389]. Treatment recommendations are based on case reports and series of cases. Historically, AmB deoxycolate was the most commonly used agent [388]. The latest literature favours the use of fluconazole or echinocandine over AmB [228, 384-386]. Fluconazole was successfully used as an initial therapy in patients with susceptible isolates, but treatment errors were also reported [390-393]. There are case reports of osteomyelitis itraconazole, voriconazole, voriconazole, and caspofungin [228, 229, 394-396]. The recovery rate appears to be significantly higher if an antifungal agent is given for at least 6 months [384, 385]. The addition of AmB deoxycolate or fluconazole to bone cement suggested that in complex cases it should be valuable as an adjunct therapy and seems safe, but this practice is controversial [397, 398]. Surgical debridement is often carried out in combination with antifungal therapy. There are reports that surgical therapy is important for candidan vertebral osteomyelitis [387], but others have not found this to be the case [388]. Surgery is recommended for patients with neurological deficits, spinal instability, large abscesses or persistent or worsening symptoms during therapy [384]. Based on some cases, Candida mediastinitis and sternal osteomyelitis in patients who have undergon sternotomy can be treated successfully with surgical debridement followed by either AmB or fluconazol [391, 399]. Irrigation of the mediastinal space amb is not recommended because it can cause irritation. Antifungal treatment with a duration of several months, similar to what is necessary for osteomyelitis in other places. What is the treatment for Candida septic arthritis? Recommendations Fluconazol, 400 mg (6 mg/kg) daily, 6 weeks OR one echinocandin (kaszpofungin 50-70 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily) for 2 weeks, followed by fluconazol, 400 mg (6 mg/ kg) daily, recommended for at least 4 weeks (strong recommendation; low quality evidence). Lipid preparation AmB, 3-5 mg/kg per day, 2 weeks, then fluconazole, 400 mg (6 mg/ kg) per day, at least 4 weeks less attractive alternative (poor recommendation; low quality evidence). Surgical drainage in all cases with septic arthritis (strong recommendation; moderate-quality evidence). In the case of septic arthritis, which contains a prosthetic device, it is recommended to remove the device (strong recommendation; evidence of moderate quality). If the prosthesis device cannot be removed, chronic suppression with fluconazole, 400 mg (6 mg/kg) per day , if the isolate is sensitive, is recommended (strong recommendation; low-quality evidence). Evidence summary Proper drainage is essential for successful therapy candida arthritis. In particular, candida arthritis of the hip requires open surgical drainage. Case reports documented cures with AmB, fluconazole and caspofungin in combination with appropriate drainage [400-402]. The use of AmB or fluconazol results in significant synovial fluid levels, so intraarticular injection of antifungal drugs is not necessary. Candida prosthetic joint infection usually requires resection arthroplasty, although the success of medical treatment alone has been described rarely [403, 404]. Combination of removal and resus implantation of the prosthesis in 2 stages, separated by 3-6 months, as well as a prolonged antifungal treatment recommended at least 12 weeks after resection atroplasty and at least 6 weeks after implantation of the prosthesis on the basis of limited data [405-407]. The effectiveness of antifungal cement keepers is contradictory [408]. If the prosthetic device can not be removed, chronic suppression of the antifungal agent, usually fluconazole, is necessary. XII. What is the treatment of Candida endophthalmitis? What is the general approach to candida endophthalmitis? Recommendations All patients with candidemia should conduct dilated retinal examination, preferably by an ophthalmologist, in non-neutropenia patients during the first week of therapy to determine whether endophtomyis is present (strong recommendation; low-quality evidence). In neutropenic patients, it is recommended to delay the study until neutrophil healing (strong recommendation; low-quality evidence). The degree of eye infection (chorioretinitis with or without macular contact, with or without vitritis) should be determined by an ophthalmologist (strong recommendation; low-quality evidence). Decisions on antifungal treatment and surgical intervention should be taken jointly by an ophthalmologist and infectious diseases doctor (strong recommendation; low-quality evidence). Evidence of summary endophthalmitis refers to infections within the eye, usually affecting the posterior ventricle and sometimes the anterior ventricle. Candida endophthalmitis can be exogenous, initially affecting the anterior ventricle and occurs after trauma or surgical intervention. More often, Candida species cause endogenous infection, in which the body reaches the posterior ventricle of the eye through hematogenous spread. Endogenous infections may occur as isolated chorioretinitis or chorioretinitis, which occurs by extending it into the vitreous body, leading to vitritis [409-412]. Candida albicans are the species most commonly responsible for endogenous endophthalmitis, but all Candida species that cause candidemia have been reported to have this complication [411-414]. In terms of visual acuity, the results depend on the degree of visual loss at the time of presentation and the involvement of macular [415]. Many principles are important in the treatment of candida eye infections. First, it is necessary to determine whether the infection includes the anterior and/or posterior segments of the eye and whether the macular or glass body is affected (70, 416-418). Achieving an adequate concentration of the appropriate antifungal agent in the eye area, which is infected, is essential for success [419, 420]. Infections affecting the chorioretinal layer are easier to treat, because this area of the posterior chamber is strongly vascular; many systemic antifungal drugs are likely to reach adequate concentrations within the choroid and retina [420-422]. Antifungal sensitivity of infected species is important. Species susceptible to fluconazole or voriconazole Whereas these active substances achieve an appropriate concentration in the posterior segment of the eye, including the glass body (419, 420, 422). Treatment should be systemic in addition to candidiaemia and eye infection for organ touch, if any. Visually threatening lesions or insanity into the vitreous body in the vicinity of the macular system generally necessitate intravital injections of antifungal agents, usually AmB doxycolate or vorikonazole, with or without vitekulus, in addition to systemic antifungal agents [412, 419, 422-425]. The ophthalmologist plays a key role in endogenous Candida endophthalmitis, deciding when and when to perform intravitreal injections and vitrectomy. The approach of a patient with candidemia has evolved over time, and normal practice now involves consulting the eye for dilated retinal examination. The recommendation to carry out an ophthalmic evaluation is not based on the result of a randomised controlled trial showing the benefits of such an assessment, but rather on a clinical assessment that the outcome of adequate treatment of absent and inadequate candidaenymitis is of great importance to the patient. The question arose as to whether ophthalmic examinations of all candidaemia patients were cost-effective [183, 426]. Members of the panel of experts believe that the risk of absence of Candida endophthalmitis outweighs the cost of obtaining an ophthalmic examination. We are concerned about the higher risk of loss of visual acuity in patients who are only examined after the manifestation of eye symptoms [415] and note that other centres report higher endophtomy rates than reports of centres questioning the routine use of eye tests [417, 418, 421]. What is the treatment of Candida Chorioretinitis without Vitritis? Recommendations for fluconazole/voriconazole sensitive isolates, fluconazole, load dose, 800 mg (12 mg/kg), then 400-800 mg (6-12 mg/kg) or voriconazole, 400 mg (6 mg/kg) intravenous dose twice a day, 2 doses, then 300 mg (4 mg/kg) intravenous or oral twice a day recommended (strong recommendation; low quality evidence). Fluconazole/voriconazole-resistant isolates, liposomal AmB, 3-5 mg/kg intravenous daily with or without oral flucytosine, 25 mg/kg 4 times daily recommended (strong recommendation; low quality evidence). Macular impresity, antifungal agents such as above-mentioned PLUS intravitreal injection or AmB deoxycolate, 5-10 µg/ 0.1 mL sterile water, or voriconazole, 100 µg/0. 1 l sterile water or normal saline solution, to ensure a rapid high level of antifungal activity is recommended (strong recommendation; low quality evidence). The duration of treatment is at least 4-6 weeks, the final duration depending on the resolution of the lesions determined by repeated ophthalmic examinations (strong recommendation; low quality evidence). Summary of evidence the greatest clinical experience in the treatment of Candida endophthalmitis was with intravenous AmB deoxycolate, just because it has been available for the longest time. However, this agent does not reach the appropriate concentration in the rear chamber [419, 420, 427, 428]. In animal studies on inflamed grains, liposomal AmB achieved higher concentrations in the eye than AmB deoxycolate or amb lipid complex [427]. Some patients were successfully treated with AmB lipids, but no concentrations in the glass body were reported [429]. Flucytosine provides complementary synergistic activity when used in AmB; should not be used as monotherapy due to the development of resistance and the reduction in the effectiveness of animal models [428]. It achieves excellent levels in the eye cases, including the glass body [412, 430]. Toxicity is common and flucytosin serum levels should be monitored weekly to prevent dose-related toxicity. Fluconazol is often used to treat Candida endophthalmitis. In experimental animals, this agent has excellent concentrations throughout the eye, including the glass body [428]. In humans, the concentration in the glass body is approximately 70 % of those in the serum [57]. Clinical and microbiological response rates in animals with experimental infections are imbolya-free, with most reports showing the efficacy of fluconazole, but some showing better efficacy of fluconazol than fluconazole [428, 431, 432]. Early human reports noted the efficacy of fluconazole, but some patients received intravitreal injections of antifungal agents, as well as systemic fluconazole [433, 434]. Despite the fact that no large published series determines the effectiveness of fluconazol therapy, this drug is routinely used to treat Candida endophthalmitis [410, 411, 415, 421]. Voriconazole plays an increasing role in the treatment of endophthalmitis [419]. Concentrations in the glass body in humans account for about 40% of serum concentrations; the medicine is relatively safe and can be administered orally or intravenously, as fluconazole [435-438]. It is more active than fluconazole against C. glabrata, although resistance increases and in some patients it can prevent its use; evenly active against C. krusei. The efficacy of voriconazole in the treatment of Candida endophthalmitis was documented but not compared with fluconazole [429, 436, 438]. Serum and (presumably) intraocular concentrations of voriconazole vary widely and serum trout levels should be routinely monitored to achieve concentrations between 2 µg/mL and 5 µg/ml in order to increase efficiency and avoid toxicity [118]. There are few data on the use of posafonazole in Candida endophthalmitis. Intraocular penetration is weak, this drug has been used in very few patients and has not been approved for the treatment of candidemia [419]. Echinocandins are first-line agents Whether chorioretinitis can be treated effectively without vitreal inclusion cannot be answered with the available data. The penetration of echinocandins into the various chambers of the eye is weak and especially weak in the glass body [412, 419, 420]. When levels were reached in humans with micafungin in experimental animal models and in a study, the doses required were higher than those currently authorised [112, 439-443]. Only a few case reports on the use of echinocandine as monotherapy have been published and the results are contradictory [444, 445]. With the availability of other active substances that have attained adequate concentrations in the glass body, there is little reason to recommend the use of echinocandins for candida endophthalmitis. Since the involvement of the macula threatens vision and the concentration of antifungal agents in the posterior chamber does not immediately reach therapeutic level, many ophthalmologists make intravitreal injections of AmB deoxycholate or vorikonzole to quickly achieve high antifungal activity in the posterior ventricle. AmB is the agent most commonly used for intravitreal injections [422, 423]. The dose of 5 to 10 µg in sterile water of 0,1 mL is generally safe [419]. Intravitreal injections of AmB lipid products in rabbits were compared with AmB deoxycolate; all preparations showed toxicity at higher doses, but at 10 µg the least toxic liposomal AmB [446], confirming an earlier study using a non-commercial liposomal product [447]. Voriconazol is increasingly used for intravitreal injections for both Candida and mold endophthalmitis [438, 448]. In animal view, it was found to be safe at concentrations of 250 µg/mL < [449]. The standard dose given to humans is 100 µg in 0,1 mL of sterile water or standard salt water (to achieve a final concentration of 25 µg/mL) [419, 438]. In vitrectomised eyes, the half-life of both AmB and voriconazole is shortened and repeated injections may be required [450, 451]. What is the treatment of Candida Chorioretinitis with Vitritis? Recommendations For the above-detailed antifungal treatment for chorioretinitis without vitritis, intravitreal injections of b-deoxycolate am-osericin B deoxololate, 5-10 µg/0,1 mL sterile water or voriconazole, 100 µg/0,1 mL sterile water or normal saline solution (strong recommendation; low quality evidence). Vitrectomy should be considered to reduce the burden on organisms and allow the removal of fungal bowls, which are not available for systemic antifungal agents (strong recommendation; low-quality evidence). The duration of treatment should be at least 4-6 weeks, the final duration depends on the resolution of lesions, which is determined by repeated ophthalmic examinations (strong recommendation; low-quality evidence). Evidence Summary candida endophthalmitis, which extended the vitreous results to worse visual results than chorioretinitis without vitritis This may be that many antifungal drugs are not able to achieve adequate concentrations in the glass body. The cause of poor results may be the increased burden of organisms in the posterior ventricle, or the existence of an abscess that can not be imagined through

vitreal haziness. Furthermore, in the case of endophthalmitis, in which fungemia is not documented and the body is unknown, vitrectomy provides a substance of culture that is better than needle aspiration and allows the appropriate antifungal agent to be used [422, 424]. Treatment, if vitritis is documented similar to recommended chorioretinitis without vitreal involvement, the added recommendations (1) are administered either AmB deoxycolate or vorikonazole in the vitreaire to achieve high drug concentrations in the posterior chamber, and (2) it is carried out pars plana vita vitectormia. Several small series noted success in patients who had early pars plana vitrectomy achieved [415, 423, 424, 452]. Removal of the vitreous body is usually accompanied by intravitreal injections of antifungal agents and, as mentioned above, the half-life of the injected antifungal agents is shortened by vitrectomy [450, 451]. The risk of retinal detachment, a serious late complication of endophthalmitis, is reduced with vitreal concern and early vitrectomy [412, 415]. For the best results, the endophthalmitis of Candida vitritis should be treated with close cooperation between the ophthalmologist and specialists in infectious diseases. XIII. What is the treatment of CNS candidiasis? Recommendations for initial treatment, liposomal AmB, 5 mg/kg daily, with or without oral flucytosine, 25 mg/kg 4 times daily recommended (strong recommendation; low quality evidence). After step-down therapy, the patient responded to initial treatment, fluconazole, 400-800 mg (6-12 mg/ kg) per day, recommended (strong recommendation; low-quality evidence). Therapy should be continued until all signs and symptoms, as well as CSF and radiological disorders, are eliminated (strong recommendation; low-quality evidence). Infected CNS devices, including ventriculostomy drains, bangs, stimulators, prosthetic reconstruction devices, and biopolymer wafers that deliver chemotherapy should be removed if possible (strong recommendation; low-quality evidence). In patients in whom the ventricular device cannot be removed, AmB deoxysolate can be injected into the chamber through the device between 0.01 mg and 0.5 mg in 2 mL 5% dextrez water (poor recommendation; low-quality evidence). Evidence Summary CNS Candida infections may occur as a manifestation of disseminated candidiasis as a complication of a neurosurgery procedure, especially when an intracranial device is inserted or rarely as an isolated chronic infection [453-462]. Meningitis is the most common appearance, but there are several small abscesses throughout the brain parenchyma, large solitary brain abscesses, and epidural [462]. Low birth weight of neonates is at high risk of cns infection, as is the complication of candidemia; neonatal cns candidiasis is addressed in the section on neonatal candida infections. Most infections occur due to C. albicans, with few reports of c. glabrata and other species causing infections [453-457, 459, 461, 462]. Treatment is based on the antifungal sensitivity of infectious species and the ability of the antifungal agent to achieve adequate concentrations in CSF and the brain. No randomised controlled studies have been conducted to evaluate the most appropriate treatment for these uncommon infections. Individual cases and small series have been reported. Most of the experience was gained using AmB deoxycolate, with or without flucytosine [453-455, 457, 459, 460, 462]. Liposomal AmB (AmBisome) has been found to reach higher levels in the brain than amphotericin B lipid complex (ABLC) or AmB deoxycolate in a rabbit model with Candida meningoencephalitis [44]. The combination of AmB and flucytosine is recommended because of the in vitro synergism noted by the combination and the excellent CSF concentration achieved by flucytosine. However, the toxic effects of flucytosin on the bone marrow and liver should be carefully monitored, preferably at frequent serum flucytosin levels. The optimal length of treatment in combination with AmB or flucytosin has not been studied. Several weeks of therapy are recommended before the transition to oral azol therapy. Fluconazole achieves excellent levels in CSF and brain tissue and has been shown to be useful as step-down therapy [453, 454, 459]. Fluconazol is also used as monotherapy; both success and failure and are therefore not recommended as first-line therapy [453, 454, 463-465]. In combination with fluconazol flucytosin, some patients [459] have been reported to cure Candida meningitis and this is a possible treatment regimen for step-down therapy. There are no reports of the use of voriconazole or posacanazole for cns candidiasis. Voriconazole achieves excellent levels of CSF and should be taken into account in the rare case of C. glabrata, which is not voriconazole resistant or C. krusei meningitis after amb treatment with or without flucytosine. Posakonazole does not reach the right concentration in CSF, and this agent is not recommended. Echinocandins have rarely been used for cns candidiasis. There are case reports of success [466], but cns breakthrough infections have been reported in patients receiving echinocandin due to candidemia [467]. There are experimental animal data noting that anidulafungin and micafungin can successfully treat C. albicans meningitis, but the doses required in humans are much higher than those currently used for candidemia [296, 299]. Currently, echinocandins are not recommended for cns candidiasis. Infected cns devices should be removed to eradicate Candida. Most of the experience with external ducts and ventriculoperitoneal goons infested with candida species [460, 463]. In recent years, infected devices include deep brain stimulators and Gliadel biopolymer wafers that have been placed in place for a brain tumor to deliver chemotherapy locally. Although difficult to remove, experience has shown that these tools should be taken out to cure infection [456, 468, 469]. Intraventricular use of antifungal drugs is usually not necessary for the treatment of CNS Candida infections. In patients with a ventricular sulcosal or external ventriculostomy removal that is too risky due to significantly increased intracranial pressure, or in patients who have not responded to systemic antifungus treatment, intraventricular AmB desoclete has been shown to be useful [453, 454, 460, 463, 469]. The dose of intraventricular AmB deoxycolate is not standardized and recommendations vary from 0.01 mg to 1 mg 2 mL 5% dextresis in water per day [455, 463, 466, 469]. Toxicity- mainly headache, nausea, and vomiting is a limiting factor when administering AmB on this pathway [454, 463]. XIV. What is the treatment of urinary tract infections due to Candida species? What is the treatment for asymptomatic Candiduria? Recommendations For the removal of predisposing factors, such as inhabiting bladder cysts whenever possible (strong recommendation; low-quality evidence). Treatment with antifungal drugs is NOT recommended, unless the patient belongs to a high-risk group; high-risk patients include neutropenic patients, infants with very low birth weight (<1500 g), and patients who have been subjected to urological manipulation (strong recommendation; low-quality evidence). Neutropenic patients and infants with very low birth weight should be treated as recommended for candidia (see sections III and VII) (strong recommendation; low-quality evidence). Patients who have had urological procedures should be treated daily with 400 mg (6 mg/kg) of oral fluconazole, or AmB deoxycolate, a daily dose of 0.3-0.6 mg/kg for a few days before and after the procedure (strong recommendation; low-quality evidence). Evidence summary of candiduria is the usual trigger for a doctor to consider whether the patient has urinary tract infection due to Candida species. The most vulnerable patients of candiduria are those who are elderly, women, diabetic, have urine-inhabiting devices, are taking antibiotics and have previously undergon surgical intervention [470-475]. Candiduria almost always means colonisation in an asymptomatic patient, and the elimination of underlying risk factors such as catheters in it is often appropriate to eliminate candiduria [471]. Several studies have found that candiduria does not often lead to candidemia [471, 472, 476-480]. Several of these studies have shown that candiduria is a marker of greater mortality, but death is not related to Candida infection and candida infection mortality rate [476, 480, 481]. A prospective study in kidney transplant patients found that although mortality was higher in patients with candiduria, the treatment did not improve the results, suggesting that candiduria was a marker of the severity of the underlying disease [482]. Many conditions require an aggressive approach to candiduria in asymptomatic patients. These include neonates of very low birth weight who are at risk of invasive candidiasis, which often includes the urinary tract [281, 483]. Many doctors who care for the treatment of neutropenic patients who have febrile and candiduria, because candiduria may indicate invasive candidiasis. However, a recent study in a cancer hospital where some patients, 25% of whom were nutropenic, found that these patients did not develop candidemia or other candiduria complications [484]. A number of reports documented the high rate of candidiasis when patients under uteriural instrumentation [485, 486], leading to recommendations for peri-treatment with antifungal drugs. What is the treatment of symptomatic Candida Cystitis? Recommendations For fluconazol-sensitive organisms, oral fluconazole, 200 mg (3 mg / kg) per day is recommended for 2 weeks (strong recommendation; moderate quality evidence). Fluconazol-resistant C. glabrata, AmB deoxycolate, 0.3-0.6 mg/kg daily 1-7 days OR oral flucytosine, 25 mg/kg 4 times a day 7-10 days recommended (strong recommendation; low quality evidence). For C. krusei, AmB deoxycolate, 0.3-0.6 mg/kg, is recommended for 1-7 days per day (strong recommendation; low-quality evidence). Removal of an indoor vesicular cystheter, if feasible, is highly recommended (strong recommendation; low-quality evidence). AmB deoxycolate bladder watering, 50 mg/ L of sterile water per day for 5 days, may be useful in the treatment of cystitis due to fluconazol-resistant species such as C. glabrata and C. krusei (poor recommendation; poor quality evidence). What is the treatment of symptomatic increasing Candida Pyelonephritis? Recommendations For fluconazol-sensitive organisms, oral fluconazole, 200-400 mg (3-6 mg/kg) per day is recommended for 2 weeks (strong recommendation; low-quality evidence). Fluconazol-resistant C. glabrata, AmB deoxycolate, 0.3-0.6 mg/kg daily for 1-7 days, with or without oral flucytosine, 25 mg/kg 4 times daily, recommended (strong recommendation; low quality evidence). In the case of fluconazol-resistant C. glabrata, monotherapy with oral flucytosin, 25 mg/kg 4 times a day for 2 weeks, (poor recommendation; low-quality evidence). For C. krusei, AmB deoxycolate, 0.3-0.6 mg/kg, is recommended for 1-7 days per day (strong recommendation; low-quality evidence). Elimination of urinary obstruction is highly recommended (strong recommendation; low quality evidence). In patients with anephrostomy tube or stent, consider removal or replacement if evidence of poor quality). Evidence Summary Candida UTI may develop on 2 different routes [487]. Most symptomatic urinary tract infections develop as a growing infection ranging from the lower urinary tract, similar to the pathogenesis of bacterial UTI. In patients with an increasing infection, there may be symptoms of cystitis or pyelonephritis. Another way of infection as a consequence of hematogenic transmission to the kidneys in a patient who suffers from candidemia. In these patients, as a rule, there is no urinary tract symptom or sign and they are treated for candidiaemia. Diagnostic tests for urine often do not help with differentiating colonization of infection, or the clarification of the affected site of the urinary tract [488, 489]. For example, pyuria in a patient with an indoor flat bladder catheter can not distinguish Candida infection from colonization. Similarly, the number of colonies in the urine, especially if the catheter is present, should not be used to determine the infection [488, 489]. Imaging of the urinary tract by ultrasound or CT is useful in determining the formation of structural disorders, hydronephrosis, abscesses, emphysematous pyelonephitis and fungal ball [490-492]. Mycelia and the pooling of yeasts (fungal balls) in the bladder or kidneys lead to blockage and preclude successful treatment of infection with antifungal drugs [94]. Rarely, Candida species cause localized infections of prostate, epididymis, or testicles [491, 493-495]. Many principles are important in the approach to the treatment of Candida UTI. The ability of the antifungal agent to achieve an adequate concentration in the urine is as important as the antifungal sensitivity of the infected species [94]. Candida albicans, the most common cause of fungal UTI, are relatively easy to treat because they are sensitive to fluconazole, which has high concentrations in the urine. In contrast, the imistic cause of fluconazol-resistant C. glabrata and C. krusei can be extremely difficult to treat. Fluconazole is a medicine used to treat Candida UTI. It was shown to be effective in eradicating candiduria in the only randomised, double-blind, placebo-controlled trial conducted in candiduria patients [496]. It is important to note that patients participating in the study were asymptomatic or had minimal symptoms of cystitis. Fluconazole is available as an oral preparation, excreted in the urine in its active form and easily reaches urine levels exceeding MIC for most Candida isolates [94]. Flucytosine demonstrates good activity against many Candida species, except C. krusei, and is secreted as an active drug in the urine [94]. Flucytosine treatment is limited by toxicity and the development of resistance when used as a single agent. AmB deoxycolate is active against most Candida species (although some C. krusei isolates are resistant) and achieves a concentration in the urine that exceeds NICs for most isolates, and even low doses have been shown to effectively manage Candida UTI [497]. The main drawback is the need for intravenous dosing and toxicity. AmB lipid preparations do not appear to reach a urine concentration suitable for UTI and should not be used [498]. All other antifungal agents, including other azol active substances and echinocandin, have minimal active drug excretion in the urine and are generally ineffective in the treatment of Candida UTI [94]. However, there have been numerous reports of patients who have been used echinocandins, mainly due to imi due to fluconazol-resistant organisms, and both success and failures [499-502] have been reported. Infection localized in the kidneys, as then the hematogenic spread, can probably be treated with echinocandins because the tissue concentration is adequate, although these agents do not reach the correct urine concentration [499]. Irrigation of the bladder with amb deoxycolate resolves candiduria in 80% to 90% of patients, as shown in a number of open studies, but in these studies recurrent candiduria was very common within a few weeks [503-505]. This approach is only useful for bladder infections and generally discourages it, especially in patients who, for other reasons, would not need a catheter [94, 506, 507]. Cystitis due to C. glabrata or C. krusei can sometimes be treated by amhotericin B bladder irrigation and endoscopic removal of possible blockage lesions [94]. What is the treatment of Candida urinary tract infection associated with fungal balls? Recommendations Surgical intervention is highly recommended in adults (strong recommendation; low-quality evidence). The above-mentioned antifungal treatment of cystitis or pyelonephritis is recommended (strong recommendation; low-quality evidence). Watering nephrostomy tubes, if any, with AmB deoxycolate, 25-50 mg of 200-500 mL of sterile water, recommended (strong recommendation; low-quality evidence). Evidence Summary Mushroom Balls is a rare complication of Candida UTI except for neonates, in whom fungal ball formation in the collection system often occurs as a manifestation of disseminated candidiasis [483]. In adults, surgical or endoscopic removal of obstructive mycelial mass plays a central role in successful treatment [94, 508, 509]. In neonates, some series documented the resolution of fungal balls with antifungal treatment [510], but others found that endoscopic removal was necessary [511, 512]. There are anecdotal reports of various techniques used to remove fungus balls from the kidney pelvis; these include endoscopic removal through a percutaneous nephrostomy tube, local infusion of streptoninase, and irrigation with antifungal drugs through a nephrostomic tube [511-513]. Fungus balls in the bladder and lower ureters can usually be removed endoscopically [509]. XV. What is the treatment of vulvovaginal candidiasis? Recommendations for uncompetative Candida vulvovaginitis, topical antifungal neither agent is better for the other, recommended (strong recommendation; high quality evidence). Alternatively, in the treatment of uncompetative Candida vulvovaginitis, a single 150 mg oral dose of fluconazole is recommended (strong recommendation; high-quality evidence). Severe acute Candida vulvovaginitis, fluconazol, 150 mg, given every 72 hours for a total of 2 or 3 doses, is recommended (strong recommendation; high-quality evidence). C. glabrata vulvovaginitis, which does not respond to oral azoles, topical intravaginal boric acid, is administered in one gelatin capsule, 600 mg daily, for 14 days is an alternative (strong recommendation; low quality evidence). Another alternative agent for C. glabrata infection is nystatin intravaginal suppositories, 100,000 units per day for 14 days (strong recommendation; low quality evidence). The third option for C. glabrata infection is topical 17% flucytosine cream alone or in combination with 3% AmB cream per day for 14 days (weak recommendation; low quality evidence). For recurrent vulvovaginal candidiasis, 10-14 days of induction therapy with topical agent or oral fluconazol, followed by fluconazole, 150 mg per week is recommended for 6 months (strong recommendation; high-quality evidence). Evidence Summary of Vulvovaginal Candidiasis can be classified as either simple, which is present in about 90% or complicated, consisting of only about 10% of cases based on clinical appearance, microbiological results, host factors, and therapeutic response [514]. Complicated vulvovaginal candidiasis can be defined as a serious or recurrent disease, an infection caused by non-albicans species and/or an infection in a pathological host. Candida albicans are the usual pathogen, but other Candida species can also cause this infection. The diagnosis of vulvovaginal candidiasis is usually clinically, when a woman presents symptoms of itching, irritation, vaginal pain, external dysuria, and dyspareunia, often accompanied by a change in vaginal discharge. Signs include vulvar edema, erythema, excoriation, cracks and white, thick, cottage cheese-like vaginal discharge. Unfortunately, these symptoms and signs are nonspecific and can result in a number of infectious and non-infectious etiology results. Before starting empirical antifungal treatment, the diagnosis should be confirmed using saline solution and 10% potassium hydroxide with wet engelen agent preparation to demonstrate the presence of yeast or hyphae and normal pH (4.0-4.5). For those who have negative results, vaginal cultures of Candida should be obtained. A variety of topical and systemic oral drugs are available for the treatment of vulvovaginal candidiasis. There is no evidence that the superiority of any topical treatment [515, 516] and oral and topical antifungal products have achieved fully equivalent results [517]. Complication-free infection can be effectively treated with any single dose or short-term fluconazole for 3 days, both reach > 90% response [517, 518]. Treatment of vulvovaginal candidiasis should not be different based on the state of human immunodeficiency virus (HIV) infection; hiv-positive and HIV-negative women are expected to have the same response rate. Complicated vulvovaginal candidiasis requires therapy to be administered intravaginally, with topical drugs for 5-7 days or by mouth, every 72 hours with fluconazol150 mg in 3 doses [54, 514]. Most Candida species, with the exception of C. krusei and C. glabrata, respond to oral fluconazole. Candida krusei reacts to all local antifungal agents. However, the treatment of C. glabrata vulvovaginal candidiasis is problematic [514, 516]. The most important decision to make is whether the presence of C. glabrata vaginal cultures reflects colonization of a patient who has another disease or indicates a real infection requiring treatment. Azol therapy, including voriconazole, is often unsuccessful [519]. Different local orders have sometimes proved effective. These include boric acid in gelatin capsules and nystatin intravaginal suppositories [520]. Topical 17% flucytosine cream can be used alone or in combination with 3% AmB cream in recalcitrant cases [520, 521]. These topical preparations, as well as boric gelatin capsules, should be aggravated by a pharmacist for special patient use. Azazole-resistant C. albicans infections are extremely rare. However, the latest evidence has emerged to document the resistance of fluconazole and azole classes in women following prolonged exposure to azol [522]. Recurrent vulvovaginal candidiasis, defined within ≥ year as 4 episodes of symptomatic infection, is usually caused by azazol-sensitive C. albicans [514, 523]. Contributing factors, such as diabetes, are rarely found. Treatment should be initiated for 10 to 14 days with induction therapy with topical agent or oral fluconazol, followed by maintenance azol treatment for at least 6 months [523-525]. The most convenient and well-tolerated treatment is 150 mg of fluconazole once a week. This treatment reaches the treatment of symptoms in >90% of patients [523]. A recurrence rate of 40% to 50% is expected after discontinuation of maintenance therapy. If fluconazol therapy is not possible, topical clotrimazole cream, 200 mg twice a week, clotrimazole inches 500 mg once a week, or other periodic oral or topical antifungal treatment is recommended [526, 527]. XVI. What is the treatment of oropharyngeal candidiasis? Recommendations Mild disease, clotrimazole troches, 10 mg 5 times a day, OR miconazol mucoadhesive tuple50 mg tablets on the mucous surface of the dog fossa once a day 7-14 days recommended (strong recommendation; high quality evidence). Alternatives to mild disease include nystatin suspension (100,000 U/mL) 4-6 mL 4 times a day, or 1-2 nystatin pastils (200,000 U 4 times a day, 7-14 days (strong medium-quality evidence). For moderate to severe disease, oral fluconazole, 100-200 mg per day, 7-14 days is recommended (strong recommendation; high-quality evidence). Fluconazole refrakter disease, itraconazole solution, 200 mg once a day OR posaconazole suspension, 400 mg twice a day for 3 days, then 400 mg daily, up to 28 days recommended (strong recommendation; moderate quality evidence). Alternatives for fluconazole-refractory disease include voriconazole, 200 mg twice daily, OR AmB deoxysole oral suspension, 100 mg/mL 4 times a day (strong recommendation; moderate quality evidence). Intravenous echinocandin (caspofungin: 70 mg loading dose, then 50 mg daily; micafungin: 100 mg daily; or anidulafungin: 200 mg load dose, then 100 mg daily) OR injecting AmB deoxycolate, 0.3 mg/kg per day, other alternative to refracter disease (weak recommendation; moderate-quality evidence). Chronic suppressive therapy is usually unnecessary. If fluconazole is recommended in patients with recurrent infection, 100 mg 3 times a week (strong recommendation; high-quality evidence). In HIV-infected patients, antiretroviral therapy is highly recommended to reduce the incidence of recurrent infections (strong recommendation; high-quality evidence). In the case of candidiasis associated with dentures, disinfection of the dentures is recommended in addition to antifungal therapy (strong recommendation; evidence of moderate quality). Evidence Summary of Oropharyngeal and Esophageal Candidiasis occurs in conjunction with HIV infection, diabetes, leukemia and other malignant tumors, steroid use, radiotherapy, antimicrobial therapy, and denture use [528, 529], and their occurrence is a recognized indicator of immune dysfunction. In HIV-infected patients, oropharyngeal candidiasis is most commonly found in patients with CD4 numbers <200 cells/μL [528-530]. The emergence of effective antiretroviral therapy has led to a dramatic decrease in the prevalence of oropharyngeal candidiasis and a significant decrease in refractory disease [531]. Fluconazole or multiazole resistance is predominantly a consequence of previous repeated and long-term exposure to fluconazole or other azol [530-533]. In particular, in patients with advanced immunosuppression and low CD4 numbers, C. albicans resistance was described as the gradual emergence of non-albicancancans Candida species, in particular C. glabrata, is a cause of refractory mucous candidiasis [532, 533]. In most cases, oropharyngeal candidiasis is caused by C. albicans, either alone or mixed infections. They described the symptomatic infections caused by C. glabrata, C. dubliniensis and C. krusei [532-534]. Several randomized prospective studies of oropharyngeal candidiasis have been conducted involving AIDS patients and cancer patients. Most patients will initially respond to topical treatment [532, 535, 536]. In HIV-infected patients, symptomatic relapses may occur sooner and fluconazole [535]. In a multicentre randomized study of HIV-infected individuals, 50 mg of mucoadhesive pital tablets of miconazol applied once a day to the mucous surface of the dog fossa were as effective as 10 mg of clotrimazole troches used 5 times a day [537]. Fluconazol tablets and itraconazole solution are better than ketochonol and itraconazol capsules [538-540]. The local effects of oral solutions can be as important as systemic effects. Posaconazole suspension is as effective as fluconazole in AIDS patients [541]. Posaconazole, a 100 mg delayed release tablet, is given 300 mg a day in one dose, approved by the FDA for prophylaxis for yeast infections in high-risk patients. The tablets provide stable bioavailability (about 55%), once-a-day injection and less stringent food requirements for absorption. This preparation has not been fully evaluated for mucous candidiasis, but, with further investigation, may replace oral suspension for this purpose. Recurrent infections typically occur in patients who have sustained immunosuppression, especially those who have AIDS and low CD4 cell counts (<50 cells/μL) [530-533]. Long-term suppressive therapy of fluconazole has been shown to be effective in preventing oropharyngeal candidiasis [53, 542, 543]. In a large multicenter study of HIV-infected patients, long-term suppressive treatment with fluconazol was compared to episodic use of fluconazol in response to symptomatic disease. Continuous suppressive therapy reduced relapses rates more effectively than intermittent therapy, but was associated with increased in vitro resistance. The incidence of refractory disease was the same in both groups [53]. Oral AmB deoxycolate, nystatin solution, and itraconazol capsules are less effective than fluconazole in preventing oropharyngeal candidiasis [544, 545]. Fluconazole refrakter infections should initially be treated with an itraconazol solution; between 64% and 80% of patients will respond to this therapy [546,547]. Posaconazole suspension is effective in approximately 75% of patients with refratonal or esophageal candidiasis [548] and voriconazole is also effective in fluconazole refrater infections [549]. Intravenous caspofungin, micafungin and anidulafungin are effective alternatives to azol agents for refractory candidiasis [24, 87, 88, 550]. Oral or intravenous AmB deoxycolate is also effective in some patients; however, the pharmacist must be complex with the oral product [551]. For the treatment of refrakter oral and esophageal candidiasis, immunomodulation was occasionally used with granulocyte macrophage colony-stimulating factor or interferon-γ occasionally for the treatment of refratory oral and esophageal candidiasis [552,553]. The decreasing rate of oral transport of Candida species and the frequency of symptomatic oropharyngeal candidiasis among HIV-infected patients are effective therapy [554]. Thus, antiretroviral therapy should be used as much as possible in HIV-infected patients with oropharyngeal or esophageal candidiasis. Chronic mucocutan candidiasis is a rare condition characterized by chronic, persistent onychomycosis and / or mucocutaneous lesions caused by Candida species. Some patients have thymoma or autoimmune polyentoconopathy syndrome type 1 [555]. Fluconazol should be used as an initial therapy for candidiasis in these patients. The response to antifungal treatment can be postponed if there is an extensive contact with the skin or nail. Due to internal immunodeficiency, most patients require chronic suppressive antifungal therapy and often develop azol-refrakter infection [556]. Patients with fluconazol-refrakter Candida infection should be treated in the same way as AIDS patients with AZOL refrakter infections [528]. XVII. What is the treatment of candidiasis of the esophagus? Recommendations Systemic antifungal treatment is always necessary. Diagnostic examination of antifungal therapy is appropriate before carrying out an endoscopic examination (strong recommendation; high-quality evidence). Oral fluconazole, 200-400 mg (3-6 mg/kg) per day, recommended for 14-21 days (strong recommendation; high-quality evidence). In patients who do not tolerate oral therapy, intravenous fluconazole, daily 400 mg (6 mg/kg) or echinocandin (micafungin, 150 mg daily, caspofungin, 70 mg loading dose, then 50 mg daily, or anidulafungin, 200 mg daily) is recommended (strong recommendation; high quality evidence). A less preferred alternative for those who do not tolerate oral therapy amb deoxycolate is 0.3-0.7 mg/kg per day (strong recommendation; moderate quality evidence). Consider de-escalating oral treatment with fluconazol 200-400 mg (3-6 mg/ kg) per day if the patient is able to tolerate oral intake (strong recommendation; moderate quality evidence). Fluconazole refrakter disease, itraconazole solution, 200 mg daily, OR voriconazole, 200 mg (3 mg/kg) twice a day intravenous or oral, recommended for 14-21 days (strong recommendation; high-quality evidence). Alternatives to fluconazol-refrakter disease include echinocandin (micafungin: 150 mg per day; caspofungin: 70 mg filling dose, then 50 mg daily; or anidulafungin: 200 mg daily) for 14-21 days, OR AmB deoxycholate, 0.3-0.7 mg/kg daily, for 21 days (strong recommendation; high-quality evidence). Posakonazole suspension, 400 mg twice a day, or extended-release tablets, 300 mg once a day, may be considered for fluconazole refrakter disease (poor recommendation; low-quality evidence). In patients who have recurrent esophagitis, chronic repressive treatment fluconazole, 100-200 mg three times a week is recommended (strong recommendation; high-quality evidence). In HIV-infected patients, antiretroviral therapy is highly recommended to reduce the incidence of recurrent infections (strong recommendation; high-quality Summary of esophageal candidiasis usually occurs in lower CD4 counts than oropharyngeal disease [528-530]. The emergence of effective antiretroviral therapy has led to a dramatic decrease in the prevalence of candidiasis in the esophagus and a significant decrease in refractory disease [531]. In most cases, esophageal candidiasis is caused by C. albicans. However, symptomatic infections caused by C. glabrata, C. dubliniensis and C. krusei have been reported [534]. The presence of oropharyngeal candidiasis and dysphagia or odynophagia in an immunocompromized host is often predictive esophageal candidiasis, although candidiasis of the esophagus can appear as odynophagia without concomitant oropharyngeal candidiasis. Therapeutic examination of patients with suspected esophageal candidiasis with fluconazole is a cost-effective alternative to endoscopic examination. In general, the symptoms of most patients with esophageal candidiasis will improve or improve within 7 days of initiation of antifungal treatment [557]. Fluconazole is better than ketochonazole, itraconazol capsules and flucytosin, and is similar to an itraconazol solution for the treatment of esophageal candidiasis [558, 559]; up to 80 % of patients with fluconazole refrakter infection respond to the itraconazol solution [547]. Voriconazole is as effective as fluconazole and has been successful in the treatment of fluconazole refrakter mucosal candidiasis [63,549]. Echinocandins are as effective as fluconazol, but are combined with higher relapse rates than those observed for fluconazole [24, 87, 88, 550]. Thus, higher doses of echinocandins are recommended for use in esophageal disease, as they are used to reduce candidemia relapses. Higher doses of micafungin [560] were tested. Fluconazole refracter disease responds to caspofungin and it is likely that micafungin and anidulafungin are as effective as caspofungin. Recurrent infections are common in patients with advanced AIDS and long-term suppressive therapy of fluconazole effectively reduces recurrence rates [53]. The use of effective antiretroviral therapy dramatically reduced the incidence of esophageal candidiasis in HIV-infected patients. Accolades The panel of experts expresses its gratitude for the thoughtful assessment of the earlier versions of Anna Thorner and Pranatharthi Chandrasekar; david van duint as liaison to the IDSA Committee on Standards and Practical Guidelines (SPGC). The panel appreciates the work of Charles B. Wessels and Michele Klein Fedyshin of the University of Pittsburgh's Health Sciences Library System to develop and implement systematic literary searches for this guidance. The financial support for the guidelines was provided by the American Society for Infectious Diseases. Potential conflict of interest The list below reflects the comparisons reported to IDSA. For the sake of thorough transparency, full disclosure of all contacts, regardless of the relevance of the subject matter of the guidelines. The assessment of such relationships as potential conflicts of interest (COI) is determined by a review process that includes an assessment of the SPGC Chairman's relationship with the SPGC Development Board, and the Board of Directors' contacts with the SPGC and, if necessary, the Directorate's COI Working Group. This assessment of possible joint judicial relations is based on the relative weight of the financial relationship (i.e. the amount of money) and the relevance of the relationship (i.e. the extent to which an independent observer can reasonably interpret the association in relation to the subject or recommendation of consideration). The reader of these guidelines should keep this in mind when the publication list is reviewed. In the case of non-work activities submitted, Mr P. G. P. served as a consultant for Merck, Astellas (past), Gilead, T2 Biosystems, Scynexis, Viamet, IMMY Diagnostics and Pfizer (past) and received research grants from T2 Biosystems, Gilead, Merck, Astellas, Scynexis and IMMY. For off-the-job activities submitted, A.A.K. received research grants from VA Cooperative Studies, Merck, the Centers for Disease Control and Prevention (CDC) and The National Institute on Aging (all past), and received royalties from UpToDate. In the case of non-work activities submitted, Mr A. was a consultant to Merck, Astellas, Pfizer, Seachaid, Mayne, Roche, Theravance, Viamet and Scynexis and received research grants from Merck, Pfizer, MSG, Actellion, Theravance, Scynexis and Atele. For activities outside the work submitted, C.J.C. consulted Merck and received research funding from Pfizer, Merck, Astellas, CSL Behring and T2 Diagnostics. 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All other authors do not report potential conflicts. All authors submitted the ICMJE form for the publication of potential conflicts of interest. Inconsistencies deemed relevant by the editors to the content of the manuscript have been made public. You can find a full list of links on the Oxford University Press website. Pocket card card