Management of Pediatric Candida Endocarditis: A Mini Review on Available Literature Between 2010-2022

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Abstract- There has been a notable rise in cases of Candida Endocarditis (CE). Even with surgical procedures and antifungal treatments, the worldwide impact of Candida on health, including morbidity and mortality, has escalated. This narrative review was carried out through the PubMed and Scopus databases, where the search terms "*Candida*" and "*Endocarditis*" were used. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, reviews, and case reports. The search was restricted to articles written in the English language from 2010 to Dec 30, 2022. Moreover, duplicate articles and non-available full-text articles were excluded. The extracted data of the search results were retrieved in this study. A background involving central venous catheters (CVC), congenital heart conditions and persistent debilitating illnesses heightens the chances of infection. Early initiation of antifungal treatment is crucial when considering Candida species and associated risk factors. The majority of research has concentrated on adult populations, leaving a gap in studies concerning pediatric patients. Presents manuscript review pediatric CE, including recent advances in management.

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Introduction

Fungal endocarditis (FE) is a rare condition, particularly in children, and is associated with significant rates of morbidity and mortality. The pediatric population shows that the prevalence of endocarditis cases related to FE falls between 0% and 12%, with an average rate of 1.1% across all cases (1). Only 1-2% of the total FE is attributed to the Candida species (spp.), and the frequency is approximately 1.5 to 4 cases per 10 million children. Due to this minimal rate, it becomes hard to detect indicators that demonstrate the beneficial treatment strategies of FE among individuals in those age ranges. The principal agent responsible for Candida endocarditis (CE) is Candida albicans, followed by Candida parapsilosis, Candida tropicalis and Candida guilliermondii (2,3), Candida krusei, and Candida stellatoidea.

Recent findings suggest a shift in the patterns of FE among individuals receiving intensive medical treatment, showing a significant connection to prosthetic heart valves and devices, as well as an extended recovery

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period after surgery. It also expands the potential chance of congestive heart failure, intravenous drug use (IVDU), catheter use, continued antibiotic cure (4) (Table 1). It has been reported that non-Candida albicans Candida (NCAC) species associated with prosthetic devices and hemodialysis drains could potentially lead to an unrelated risk factor in CE (5). Such as C. parapsilosis, which can be transmitted via contaminated central venous catheter (CVC) and cause infection in neonates (6). This is a mini review, containing the latest evidence and scientific advances in pediatric CE management.

Table 1. Risk factors associated with developing fungal endocarditis pediatric patients

Congenital heart defects (CHD)
Ventricular septal defect (VSD)
Atrial septal defect (ASD)
Aortic stenosis (AS)
Patent ductus arteriosus (PDA)
Tetralogy of Fallot (TOF)
Cardiac valve abnormalities (CVA)
Mitral valve prolapses (MVA)
Corrective or palliative surgery for heart defects
Vascular patches, vascular grafts, prosthetic valves
Parenteral hyperalimentation,
Multiple broad-spectrum antibiotics
Chronic immunosuppression
Premature infant with a low birth weight
Candidemia in the neonate
Transplantation
Rheumatic heart disease (RHD)
Double outlet right ventricle (DORV)
Leukemia
Immunocompromised

Materials and Methods

This narrative review was carried out through the PubMed and Scopus databases, where the search terms "*Candida*" and "*Endocarditis*" were used. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, reviews, and case reports. The search was restricted to articles written in the English language from 2010 to Dec 30, 2022. Moreover, duplicate articles and non-available full-text articles were excluded. The extracted data of the search results were retrieved in this study.

Treatment option and in vitro finding

There are multiple categories of antifungal drugs that can be used to manage invasive infections. Most antifungal agents inhibit the production of ergosterol, cause damage to the cytoplasmic membrane, interfere with DNA and RNA synthesis, and alter the structure of the cell wall (Figure 1).

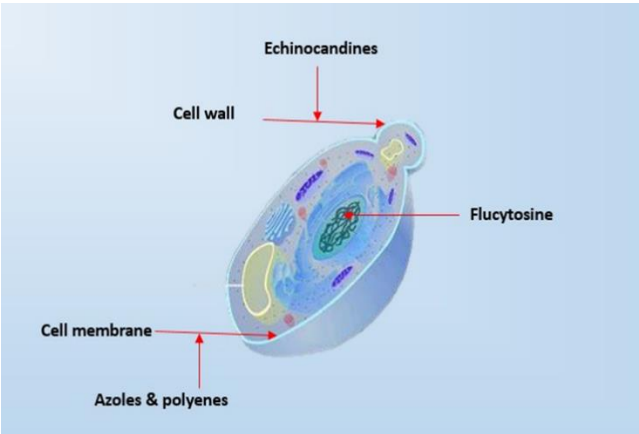

Figure 1. Mechanisms of action of antifungals against Candida spp

Polyenes

Polyenes represent the earliest category of antifungal drugs that gained significant usage, with Amphotericin B as the key medication in this class. It attaches to ergosterol in the cytoplasmic membrane, reducing its structural integrity. Furthermore, it aids in the formation of pores, leading to the release of substances from within the cell and ultimately resulting in cell death (7). The fungicidal properties of Amphotericin B are associated with the induction of oxidative stress (7,8). Amphotericin B in lipid-based formulations greatly reduces its harmful side effects, allowing for higher dosage administration (9).

Azoles

Azoles affect the ergosterol production process by inhibiting the enzyme lanosterol 14α-demethylase, which decreases ergosterol levels and causes other sterols to accumulate to harmful levels, ultimately altering membrane permeability. Azoles have a fungistatic effect.

Azole antifungals were classified into imidazoles (miconazole, ketoconazole and clotrimazole) and triazoles (fluconazole, itraconazole, voriconazole and posaconazole) groups. Among the azole antifungals, fluconazole stands out for its high oral bioavailability, making it a preferred choice for managing invasive candidiasis. The minimum inhibitory concentration (MIC) of fluconazole for *C. albicans* strains differs, ranging from 0.25 to 8 µg/ml. *Candida krusei* has intrinsic resistance to fluconazole, while for *C. glabrata* strains the MIC values of fluconazole were (8 to 64 µg/ml) revealing poorer susceptibility to fluconazole (10). Voriconazole displays higher fungistatic activity against *C. krusei* and *C. glabrata* (10). The MIC range of itraconazole against *C. albicans* strains is between 0.03 and 0.5 µg/ml (10).

Echinocandins

Echinocandins act by inhibiting the synthesis of β-1,3 glucan, an essential component of the cell wall. This antifungals class has fungicidal activity against *Candida* spp. Caspofungin, micafungin, and anidulafungin can be administered through intravenous injections. The wide-ranging spectrum of activity of these drugs is the same, the MICs values between 0.03 and 1 µg/ml for most of *Candida* spp (11).

Flucytosine

Flucytosine, a fluorinated form of pyrimidine, was initially developed as a treatment for cancer, but it also exhibits antifungal effects. After fungal uptake of flucytosine, it is converted into 5-fluorodeoxyuridine monophosphate and 5-fluorouridine triphosphate. The former metabolite inhibits DNA synthesis, and the latter is incorporated into RNA, inhibiting protein synthesis. It is used in second- or third-line therapy and is often administered in combination with amphotericin B to prevent a rapid emergence of resistance. The MICs of flucytosine for *Candida* spp. are between 0.06 and 1 µg/ml (12,13).

What is the treatment for candida endocarditis (14)?

I. Natural valve endocarditis was treated as follows:

II. a) Amphotericin B (lipid formulation) (LAMB), 3-5 mg/kg once daily, alone or in combination with flucytosine, 25 mg/kg, 4 times a day, L-AMB can be used in cases of Candida endocarditis in pediatric patients where non-surgical treatment is preferred (15,16).

b) High doses of caspofungin (150 mg/d), micafungin (150 mg/d), or anidulafungin (200 mg/d) are recommended for early management.

III. Switching from IV to oral antifungal therapy with fluconazole, 400-800 mg (6-12 mg/kg) daily, is optional for individuals infected with susceptible isolates *of Candida* spp., who have exhibited stability of vital signs, and have cleared *Candida* spp. from the bloodstream.

IV. For isolates resistant to fluconazole, substitution with oral voriconazole, 200-300 mg (3-4 mg/kg) twice a day, or posaconazole tablets, 300 mg once daily, is recommended.

V. Valve replacement surgery is suggested; antifungal therapy should be continued for at least 6 weeks post-operation and for a longer period in patients with perivalvular abscesses or other complications (17).

VI. For patients who are not candidates for surgical replacement, long-term therapy with fluconazole (if the isolate is susceptible), 400-800 mg (6-12 mg/kg) once a day, is optional.

VII. In case of prosthetic valve endocarditis, similar therapeutic management strategies proposed for native valve endocarditis cases are optional.

VIII. Fluconazole, 400-800 mg (6-12 mg/kg) daily, is suggested to prevent relapses.

IX. In cases where patients continued to exhibit candidaemia and thrombocytopaenia following three weeks of conventional antifungal treatment, recombinant tissue plasminogen activator (rtPA) is an option to resolve the vegetations(18-21).

X. Patients who have large vegetations (over 15 mm)

should be prioritized for surgery within a few days, and those with fungal infections that resist medical intervention should be treated surgically during their hospitalization (22).

What is the treatment for Candida infection of implantable cardiac devices (14)?

Table 2 discusses the following information: Medical history, causative fungal agents, treatment regimes, and outcomes of pediatric fungal endocarditis cases between 2010-2022.

I. In cases involving pacemakers and implantable cardiac defibrillators, it is essential to entirely extract the device.
II. For ventricular assistance devices that are non-removable, the optimal antifungal management approach is comparable to the guidelines established for endocarditis involving natural heart valves.
III. Maintenance therapy with fluconazole (if the isolate is susceptible), is crucial in cases, when the device is not extracted.

Why is it hard to treat a CE?

One of the initial obstacles in treating CE is the resistance to antifungal therapies. *Candida* spp. acquired resistance due to the raised consumption of wide-spectrum antifungals. Numerous global studies highlight the rising incidence of *Candida* resistance to the most widely utilized antifungal agents. For instance, Mutations that affect amino acids in the hotspot (HS) region of the *ERG11* gene can initiate resistance to azole antifungals (23). Thus, these fungi exhibit reduce susceptibility to antifungals, needing higher dosage because of an increase in the MIC. This represented as clinical resistance where an increased dosage beyond the standard is necessary to eliminate the pathogen. To address this issue, performing *in vitro* antifungal susceptibility tests is suggested to determine which antifungals are ineffective, indicating resistance. There is a notable rise in azole resistance among *Candida* species, linked to the overactivity of MDR genes that code for efflux pumps, which effectively eliminate azoles from the cells (24). *C. parapsilosis* and *C. guillermondii* are known to carry mutations in *FKS1* gene (25). The most common mechanisms responsible for echinocandin resistance in *C. glabrata* is the mutations in *FKS1*'s *HSP1* (Phe625, Ser629) and *FKS2* (Phe659, Ser663). *C. parapsilosis* display antifungal resistance to a multiple agent, emphasizing the complicatedness in handling NAC endocarditis (26). Fluconazole may also face multidrug resistance, along with a decrease in susceptibility to echinocandins, especially in the strains of *C. glabrata* and *C. krusei* (27).

On the other hand, *Candida* spp. is able to create biofilms on various medical devices, including vascular catheters, prostheses, endotracheal tubes, cardiac valves and pacemakers, which considered as a significant contributor to the widespread antifungal resistance through the production of extracellular matrix (ECM). By offering mechanical defense to biofilms, this ECM prevents external structural damage and curtails the diffusion of antifungal agents at the site of infection. Amphotericin B exhibits a fungicidal effect on *C. albicans* biofilms that is dependent on the dosage used (28,29). However, lipid formulations of this drug can address this issue, as they demonstrate inhibitory effects on biofilms at the same minimum inhibitory concentrations (MICs) as seen in planktonic cells (0.25 to 1 µg/ml) (30). The lipid formulations of amphotericin B showed full eradication of catheter- related *C. albicans* biofilms (31).

The effect of antifungal therapy of planktonic and sessile cells is dissimilar, the latter display more antifungal resistance. Voriconazole (256 µg/ml) and posaconazole (64 µg/ml)) show no effectiveness against Candida biofilms (32). However, at a concentration of 2 µg/ml, caspofungin exhibits a fungicidal effect on *Candida* spp. biofilms, regardless of their developmental stage (33). Combination therapy of fluconazole or amphotericin B with caspofungin had no synergistic outcome against *C. albicans* biofilms.

Prophylaxis and prevention

There is insufficient scientific proof supporting the effectiveness of preventive measures against infective endocarditis (IE) (34). The 2009 guidelines from the European Society of Cardiology (updated in 2015) have led to a considerable reduction in the use of antibiotic prophylaxis, which is now suggested only for those patients who are at the highest risk for developing infective endocarditis (IE). High-risk pediatric patients include those with homografts, a history of IE, untreated cyanotic congenital heart disease, or congenital heart disease involving postoperative palliative shunts, conduits, or prosthetic materials (35).

A study by Ağın *et al*., identified risk factors for Candida infections in pediatric ICU settings, such as prolonged ICU stays, mechanical ventilation, central venous catheters, and total parenteral nutrition. Decisions about antifungal prophylaxis should be individualized, particularly for high-risk patients with extended ICU stays (>21 days), poor response to empirical antimicrobial therapy, or immunocompromised

conditions. Strict aseptic techniques are crucial during venous catheter manipulation and invasive procedures to reduce healthcare-associated IE (34,36).

Prophylactic treatments ought to focus solely on patients at high risk who exhibit considerable predisposing factors; however, preventive strategies should be applied to all individuals, particularly those with existing heart issues or artificial devices (34).

While Candida-related infective endocarditis is rare and often deadly in children, it is essential to routinely conduct echocardiograms for those with positive blood or catheter cultures indicating Candida presence. In selected cases, rapid and successful antimicrobial intervention might make cardiac surgery unnecessary, yet this cannot be generalized to all patients (1). The deaths of the patients were associated with complications from septicemia and/or embolism (37).

Prognosis

The occurrence of multidrug-resistant bacterial infections in conjunction with Candida species in infective endocarditis, children diagnosed with lymphohemophagocytic syndrome (LHFS) or those who have undergone surgery for endocardial vegetation, might be seen as poor prognostic markers (38).

Pediatric *Candida* endocarditis is a chronic disease, which is complicated to handle due to the multifactorial nature of the infection. The existing global consequence of CE in pediatrics influences the medical team to reconsider the existing diagnostic approaches and develop therapeutic strategies. Precise diagnosis is essential to identify the exact etiological agent to start medication. New medication, combinational treatment, prophylaxis, post-treatment and the addition of compounds affecting *Candida* biofilms should be considered for effective management of CE.

Table 2. Medical history, causative fungal agents, treatment regimes, and outcomes of cases of pediatric fungal endocarditis between 2010-2022

Study	Age	Sex	Underlying Condition	Site	Fungi Species	Treatment	Outcome
Kumar et al. 2010 (2)	5-Year-old	F	PICU station, BSA therapy, CVC, CD, large right-sided heterogeneous vegetations.	TVE	*C. tropicalis*	1.FCZ (IV:12 mg/kg followed by 10 mg/kg/day); **not response** 1- LAMB (3 mg/kg/day, gradually increased to 5 mg/kg/day (5 weeks) **Not response** 2- surgical removal of the entire vegetation with total tricuspid valve (TV) excision 3- LAMB was continued for 2 weeks postoperatively (total 7 weeks of therapy).	Cure with surgery and post-operative treatment with LAMB (2 weeks)

Azhar 2012 (39)	14-day-old infant	F	Prematurity; very low birth weight of 1400 g, intravenous ampicillin and gentamicin for 5 days; NICU; Intravenous fluids and broad-spectrum intravenous antibiotics, ampicillin and cefotaxime,	Left and right ventricles.	*C. albicans*	Ampicillin and cefotaxime were discontinued and were replaced with 1- intravenous fluconazole (6 mg/kg/day) and amphotericin B lipid complex	Cure with combination treatment with fluconazole IV a LAMB N (8 weeks) (10 mg/kg/day).
Jajoo *et al*, 2012 (40)	Term	M	CVC; respiratory distress; cefotaxime and amikacin uptake;	Right ventricle.	*C. tropicalis*	1-Injection amphotericin B, however icterus didn't improve and no weight gain occurred over next two weeks. 2-Combination of LAMB and FCZ	Baby received total six weeks of liposomal amphotericin B and fluconazole. Cardiothoracic surgical opinion was sought, and was advised to continue with conservative therapy. Since the appearance of vegetations in echocardiography remained stable, gall bladder masses disappeared, hepatitis recovered completely, and baby started gaining weight adequately; he was discharged on long term prophylaxis with oral fluconazole. On serial follow ups over next 1.5 years
Cetin *et al*, 2013 (41)	28 weeks born infant	F	Prematurity; very low birth weight of 980g; cefotaxime (100 mg/kg/day, two doses) plus amikacin (18 mg/kg/dose, in every 35 hours); respiratory distress syndrome	Right atrium)	*C. tropicalis*	1-Lamb (6 mg/kg/day, one daily dose).	Cure with Lamb (in total 60 days)
Chaudhary *et al*, 2013 (42)	7-year-old	M	T-cell acute lymphoblastic leukemia, was started on chemotherapy with the MCP-841 protocol. After induction, he achieved remission. He received two cycles of high-dose cytarabine [dosage and route not stated], and he underwent repeat induction. After receiving cytarabine, he developed febrile neutropenia. He also developed necrotising cellulitis; amikacin and piperacillin/tazobactam. In the ensuing days, he developed severe neutropenia, and thantibacterial and antifungal therapy. The	Tricuspid Valve	*C. albicans*	NU	Surgery with excision of the vegetations. After the surgery, he developed acute renal failure, refractory septic shock and metabolic acidosis. He died on the third postoperative day [cause of death not stated].

Abdurrahman *et al*, 2016 (43)	27th week infant	M	neutropenia resolved, but the fever persisted Prematurity; birth weight; bactrial endocarditis; catheter; small ASD; antibutic therapy for 16 days; CVC	Atrial septal	*C. albicans*	1-Flucoazole for 2 weeks 2- AMB for 7 weeks	
Oner et al. 2017 (44)	7-year-old	M	Surgery for tetralogy of Fallot at 5 years, hospitalised for placement of a pulmonary bioprosthesis and tricuspid valve repair	right ventricle vegetations/ Pulmonary involvement	*C. albicans*	1- Surgical remove of bioprothesis 2- Fluconazole and AMB 5mg/kg/day for 6 weeks 3- Fluconazole 5mg/kg/day continued lifelong	Cure and fungal lesions disappearance
Babazadeh *et al*, 2018 (45)	17-year-old	M	Bacterial endocarditis; history of cardiac manipulation	Mitral valve	*C. albicans*	Surgery of mitral valve was replaced and fungal mass was completely removed.	Dide due to acute heart failure and uncontrolled sepsis
Vanhie *et al*, 2019 (46)	11-year-old (CE at bithday)	F	Premature at birthday; birth weight of 1310 kg	Right ventricular	*C. albicans*	Fluconazole therapy	Cure
Portillo-Miño *et al*, 2020 (47)	3 months infant	Low weight birth 2900g	NM	Rieght atrium	*C. lusitaniae*	FCZ	
Gourav *et al*, 2021 (48)	Two-year-old	M	Respiratory distress and recurrent respiratory tract infections for two months of age	Ventricular septal defect (VSD)	*C. tropicalis*	Injection liposomal Amphotericin B (5 mg/kg/day) and IV Fluconazole (12 mg/kg loading dose followed by 6 mg/kg/day). After two weeks of therapy	Cure with lamb (8 weeks)
Salehi-ardebili *et al*, 2013 (49)	4-year-old	F	Acute Lymphoblastic Leukemia	E tricuspid valve	*C. albicans*	Surgical excision of the vegetation and intravenous liposomal amphotericin B for 3 weeks	
Vassileva *et al*, 2022 (50)	3-month-old	F		Mitral valve	*Candida spp.*	A valve-sparing operation with complete removal of the fungal vegetations, a relapse with complete destruction of the valve leaflets and severe mitral regurgitation with decompensated heart	

							failure occurred three months later After 10 days of combined antifungal therapy with amphotericin B and fluconazole (six weeks in total) A second operation with successful mitral valve replacement was performed amphotericin B and voriconazole was started

PICU; broad-spectrum antibiotic: BSA; central venous catheter: CVC; chest drainage: CD; Tricuspid valve endocarditis: TVE; fluconazole: FCZ; liposomal amphotericin B: LAMB; atrial septal defect (ASD)

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