Interactive CardioVascular and Thoracic Surgery 23 (2016) 431–437
doi:10.1093/icvts/ivw156 Advance Access publication 24 May 2016

Cite this article as: Jaworski R, Haponiuk I, Irga-Jaworska N, Chojnicki M, Steffens M, Paczkowski K *et al*. Fungal infections in children in the early postoperative period after cardiac surgery for congenital heart disease: a single-centre experience. Interact CardioVasc Thorac Surg 2016;23:431–7.

Fungal infections in children in the early postoperative period after cardiac surgery for congenital heart disease: a single-centre experience

Radoslaw Jaworski[a,*], Ireneusz Haponiuk[a,b], Ninela Irga-Jaworska[c], Maciej Chojnicki[a], Mariusz Steffens[a], Konrad Paczkowski[a] and Jacek Zielinski[d]

[a] Department of Pediatric Cardiac Surgery, Copernicus Hospital, Gdansk, Poland
[b] Chair of Physiotherapy, Gdansk University of Physical Education and Sport, Gdansk, Poland
[c] Department of Pediatrics, Hematology and Oncology, Medical University of Gdansk, Gdansk, Poland
[d] Department of Surgical Oncology, Medical University of Gdansk, Gdansk, Poland

[*] Corresponding author. Department of Pediatric Cardiac Surgery, Copernicus Hospital, Al. Jana Pawła II 50, 80-462 Gdansk, Poland. Tel: +48-58-7684881; e-mail: radicis@go2.pl (R. Jaworski).

Received 30 December 2015; received in revised form 18 April 2016; accepted 21 April 2016

Abstract

OBJECTIVES: Postoperative infections are still an important problem in cardiac surgery, especially in the paediatric population, and may influence the final outcome of congenital heart disease treatment. Postoperative infections with fungi are uncommon. The aetiology is poorly understood, and the proper diagnosis and treatment is unclear. In this single-centre study, the frequency of invasive fungal disease in children who underwent surgical management of congenital heart diseases was determined along with the risk factors for infection, treatment options and outcomes.

METHODS: All consecutive paediatric patients (<18 years of age) who underwent cardiac surgery for congenital heart disease between September 2008 and December 2015 in a paediatric cardiac centre in Poland were identified. Those who developed invasive fungal disease in the early postoperative period (30 days) were identified.

RESULTS: Of the 1540 cardiosurgical procedures for congenital heart disease, 6 were complicated by fungal infection (0.39%). One patient had a high probability of fungal infection, but the diagnosis was unproved. Nevertheless, the patient was successfully treated with antifungal treatment. Five had proven invasive fungal disease. Of these, 3 were diagnosed with candidaemia. All had undergone cardiopulmonary bypass. Of the remaining 2 patients, 1 was a preterm newborn with complete atrioventricular septal defect who developed rib fungal invasion. The remaining patient had pulmonary atresia with ventricular septal defect and developed Fournier's gangrene after surgery. None of the patients died due to infection in the early postoperative period. However, the child with rib fungal invasion died 39 days after surgery as a result of multiorgan failure.

CONCLUSIONS: Fungal infections in paediatric patients after cardiac surgery may markedly influence morbidity and mortality. Fungal infection prophylaxis in this specific group of children may reduce morbidity, whereas early empirical treatment followed by a targeted approach may improve outcomes. The 'hit fast, hit hard' treatment strategy may be the best rescue option for children who develop invasive fungal disease after cardiac surgery.

Keywords: Invasive fungal disease • Candidemia • Candida albicans • Pediatric cardiac surgery • Fournier gangrene

INTRODUCTION

In modern healthcare, many types of invasive devices and procedures are used to diagnose and treat diseases. This can increase the risk of hospital-acquired infections. This is particularly problematic given that the worldwide abuse of antibiotics has influenced human microbiota and promoted the development of multidrug resistance. Indeed, antibiotic abuse has changed the epidemiology of postoperative infections in surgery.

These problems are particularly acute in cardiac surgery, which differs from other surgical fields in that it involves many invasive therapeutic procedures, cardiopulmonary bypass is often needed, and the treatment is often complex and requires long operation times. Moreover, the patients must often stay in the postoperative intensive care unit for long periods of time. These factors elevate the risk of postoperative infections, especially in the paediatric population. This can influence the treatment outcomes of congenital heart diseases.

Various pathogens are responsible for postoperative infections after paediatric cardiac surgery. However, fungal infections are rare: the incidence of fungal infections in surgically treated cardiac patients ranges from 0.2 to 0.35% [1, 2]. The most common aetiological agent is *Candida*. Notably, Abou *et al*. [3] showed that the mortality rates of patients who develop invasive fungal disease (IFD) in the postoperative period range from 39 to even 100%. It may be that these mortality rates vary so widely because different

fungal species or strains predominate in different centres. However, despite these studies and the potential gravity of IFDs, the aetiology of these infections and how to diagnose and treat them remain poorly understood.

This study aimed to highlight the problem of fungal infections in the early postoperative period in children undergoing cardiac surgery for congenital heart defects. The study site was a paediatric cardiac centre. The frequency of IFD in these patients was determined along with its risk factors, treatment options and final outcomes.

MATERIALS AND METHODS

Identification of cases of postoperative invasive fungal disease

The medical records of the Department of Pediatric Cardiac Surgery were searched to identify all consecutive cardiac surgeries on children (newborns and older children <18 years of age) with congenital heart disease over an 8-year period (September 2008 to December 2015). The patients who developed an IFD in the early postoperative period (30 days) were identified.

The surgeries were performed with or without extracorporeal circulation (ECC). In the patients who underwent surgery with ECC, hypothermia ranging from 16 to 32°C was induced and was mainly accompanied by aorta cross-clamping. Some patients were treated with deep hypothermic circulatory arrest.

IFDs were detected as follows. At admission to our department, all patients underwent culture sampling of the nose, pharynx, anus, groin and, in newborns, the ears to determine the preoperative microbiological colonization status at these sites. Materials from at least three of these body sites were tested for the presence of multidrug resistance bacteria and *Candida* colonization; for this, routine microbiological culture and identification methods were used. In the postoperative period, we followed the accepted algorithm in our department, namely, when a child was suspected to have an infection, specimens were taken and were subjected to microbiological and biochemical examinations. When septicaemia was suspected, at least two blood samples from different venous locations were taken. When focal infection was suspected, material from the location was taken. If blood, tissue or bone aspirate samples were positive for microbiological culture, routine microbiological methods were used to assess drug sensitivity according to the EUCAST guidelines. IFD of any aetiology in the early postoperative period was categorized according to the revised definitions of IFD published in 2008 by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group [4]. These definitions categorize the diagnosis of IFD as 'proven', 'probable' and 'possible'. IFD diagnosis is considered to be proven for most conditions of IFD when fungal elements are detected in the diseased tissue. An IFD diagnosis is considered probable when one or more host factors and one or more clinical features are observed together with evidence of mycological infection. An IFD diagnosis is considered possible when mycological evidence is lacking, but one or more host factors are observed together with sufficient clinical evidence that is consistent with IFD. In addition, we considered that patients with a Candida score of ≥3 points had a high probability of fungal infection, as described by Leon *et al*. [5].

Data analyses

The patients with IFD were assessed for the presence of the following risk factors for fungal infection: prematurity, neutropaenia, preoperative *Candida* colonization, treatment with immunosuppressive agents, antacid treatment, parenteral nutrition, presence of primary and/or secondary immune deficiencies, prolonged antibiotic therapy (>5 days), prolonged endotracheal intubation (>3 days), prolonged central vascular catheterization (>7 days), prolonged catecholamine support, the sternum was left open during the postoperative period, the patient had implantable prosthetic devices and renal replacement therapy [6, 7]. The clinical course of the IFD in each affected child during early and late postoperative follow-up was analysed, particularly the details of antifungal treatment.

RESULTS

During the study period, 1540 cardiac surgical interventions were performed in paediatric patients: 736 with and 804 without ECC support (Fig. 1). Six patients had fungal infections in the early postoperative period (0.39%). One patient did not meet the criteria for either probable or possible IFD, as defined by EORTC/MSG. However, this patient had a high probability of fungal infection, as indicated by the Candida score, and was successfully treated with antifungal agents. In the remaining 5 patients, the IFD was proved. Three had postoperative candidaemia, as indicated by multiple blood cultures of *Candida*. One patient had primary sterile tissue invasion with *Candida albicans* in the left rib. The remaining patient with proven IFD had Fournier's gangrene that was caused by *C. albicans* (Fig. 2).

Regarding the remaining 1534 procedures, thorough microbiological postoperative diagnostics did not detect any signs of fungal infection. There was also no sepsis-related mortality in this group of patients.

The demographics, surgical procedures and clinical characteristics of the 5 patients with proven IFD are summarized in Table 1. Three patients developed proven IFD (candidaemia) after surgery

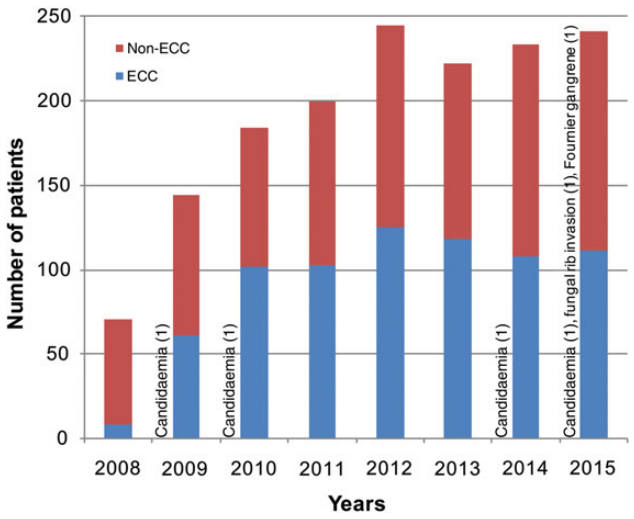

Figure 1: Surgical procedures in children with congenital heart disease in the Department of Pediatric Cardiac Surgery, Gdansk, Poland. ECC: procedures with extracorporeal circulation support; non-ECC: procedures without extracorporeal circulation support.

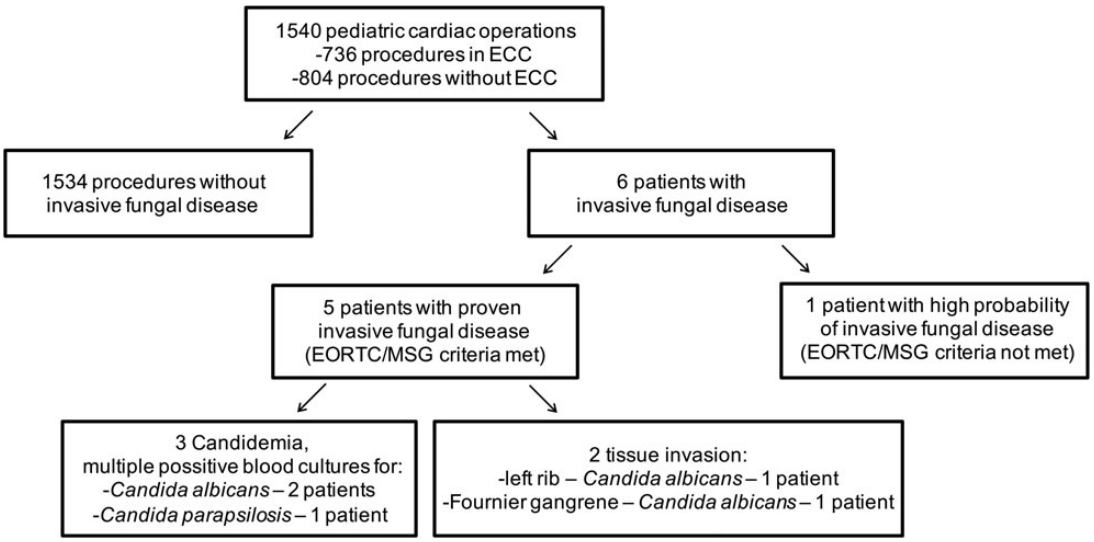

Figure 2: Diagram showing patients with invasive fungal disease treated cardiosurgically in the Department of Pediatric Cardiac Surgery, Gdansk, Poland. ECC: procedures with extracorporeal circulation; EORTC/MSG: European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.

Table 1: Demographics, surgical procedure and clinical characterization of children with congenital heart disease with proven invasive fungal disease treated surgically in Gdansk in the years 2008–2015

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at surgery	20 months	8 months	3 months	5 weeks	4 weeks
Gender	Female	Male	Female	Male	Male
Weight (kg)	9	6	3.4	2.4	3.1
Prematurity	No	No, but hypotrophy at birth (2.9 kg)	No, but hypotrophy at birth (2 kg)	Yes (33 weeks, 1.9 kg)	No, but hypotrophy at birth (2.7 kg)
Candida colonization	Yes	–	Yes	–	Yes
Primary diagnosis	DORV + CoA	ToF	VSD, ASD II	AVSD, HF	PA-VSD
Additional diagnosis	–	Hypothymia, dysmorphia, polydactylism	–	Hypothymia, Down syndrome	–
Antifungal prophylaxis	Fluconazole	Fluconazole	–	Fluconazole (as empirical treatment)	–
Previous surgical procedures	CoA repair + PA banding	–	–	–	–
Cardiosurgical procedure	DORV repair (intraventricular tunnelization with Dacron® patch), debanding PA	ToF repair using xenograft (Contegra®, USA) for RVOT plasty (monocusp)	VSD closure, reoperation 2 days after (aortic insufficiency)	PA banding, PDA closure	Unifocalization, aortopulmonary shunts bilateral (Gore-Tex®)
ECC	Yes	Yes	Yes	–	–
ECC time (min)	240	195	180	–	–
DHCA	–	–	Yes	–	–
AoX (min)	150	75	41	–	–
Hypothermia	28°C	28°C	20°C	–	–

DORV: double outlet right ventricle; CoA: coarctation of aorta; ToF: tetralogy of Fallot; VSD: ventricular septal defect; ASD II: atrial septal defect type II; AVSD: atrioventricular septal defect; HF: heart failure; PA-VSD: pulmonary atresia with ventricular septal defect; PA: pulmonary artery; RVOT: right ventricular outflow track; ECC: extracorporeal circulation; DHCA: deep hypothermic circulatory arrest; AoX: aortic cross-clamping.

with ECC: the mean ± standard deviation bypass and aorta cross-clamping times were 205 ± 31 (range, 180–240) min and 89 ± 56 (range, 41–150) min, respectively.

Table 2 indicates the risk factors for fungal infection in the 5 patients with proven IFD. The risk factors of the 3 patients who underwent surgery with ECC were mainly related to postoperative low cardiac output syndrome. This resulted in secondary immune deficiency and the need for extended intensive treatment. Three patients with proven IFD were preoperatively colonized with *Candida*: in 2, fluconazole prophylaxis was initiated on post-operative day 2. In 1 patient, the sternum was left open for 2 days after surgery. For all 5 proven cases, the mean intervals between

Table 2: Risk factors for fungal infection in children with congenital heart disease with proven invasive fungal disease treated surgically in Gdansk in the years 2008–2015

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Prematurity	–	–	–	+	–
Neutropenia	–	+	–	–	
Candida colonization	+	–	+	–	+
Immunosuppressive agents	–	–	+	–	–
Antacids	+	+	+	+	+
Parenteral nutrition	+	+	+	–	+
Primary immune deficiencies	–	+	–	+	–
Secondary immune deficiencies	+	+	+	+	+
Prolonged catecholamine support (>2 days)	+	+	+	+	–
Prolonged antibiotics (>5 days)	+	+	+	+	–
Prolonged endotracheal intubation (>5 days)	+	+	+	+	+
Prolonged central vascular catheterization (>7 days)	+	+	+	+	+
Sternum left-opened	+	–	–	–	–
Implantable prosthetic devices	+	+	+	+	+
Renal replacement therapy	+	+	+	–	–
Sum of risk factors	11/15	10/15	12/15	9/15	7/15

clinical onset and total parenteral nutrition, antibiotic administration and endotracheal intubation were 10 ± 1 (range, 9–11), 11 ± 1 (range, 10–12) and 11 ± 1 (range, 10–12) days, respectively. Three patients needed 3, 7 and 10 days of renal replacement therapy after surgery, respectively. The patient with fungal rib infection underwent emergency surgery during active infection due to heart failure and deterioration of the general health status. At that time, the aetiology had not yet been identified. The patient with Fournier's gangrene had low postoperative cardiac output that resulted in systemic hypoperfusion and presumably secondary immune deficiency.

In the 3 patients with candidaemia, the median day of clinical onset was the 11th postoperative day (Days 10, 11 and 12, respectively). In each case, that was the day that the blood samples were taken for microbiological analysis. These analyses later confirmed that the patients had IFD. On the day of clinical onset, the mean ± standard deviation C-reactive protein (CRP) level was 44 ± 21.1 (range, 24–66) mg/l. The mean ± standard deviation change in CRP between IFD onset and the day before was 28 ± 12.3 (range, 19–42) mg/l. In these 3 patients, eight blood samples in total were taken on the day of onset (two, two and four samples, respectively): all samples confirmed infection with *Candida*. In 2 patients, the responsible pathogen was *C. albicans* and in 1 patient *C. parapsilosis*. One patient with candidaemia developed fungal organ invasion: an ultrasound examination 2 days after IFD onset indicated typical fungal infection lesions in both lungs.

The *C. albicans* rib invasion was confirmed by microbiological examination of intraoperative tissue sample taken from the left rib. The patient was a 5-week-old preterm and hypotrophic boy with congenital heart disease, namely, complete atrioventricular canal and trisomy of the 21st chromosome. He was admitted as an emergency to our department with heart failure and an active infection of unknown origin. He received antibiotics and was treated with fluconazole for a few days. At this point, his CRP level was 132 mg/l and his procalcytonin (PCT) level was 0.74 ng/ml. He qualified for life-saving palliative treatment, namely, the pulmonary artery banding procedure. During left thoracotomy and preparation of the intercostal space with electrocautery, the rib periosteum was cut and yellow-reddish fluid leaked from the rib. Its consistency was bone marrow-like, but it had an unusual colour. The sample was taken for microbiological analysis. After 2 days, *C. albicans* was isolated in the sample. Since the patient had been transferred to another centre on the first postoperative day, the antifungal treatment was started there. The child was treated with voriconazole, although multiple blood samples obtained later in the postoperative period were negative for fungi. Unfortunately, after 39 days, the patient died due to multiorgan failure. The autopsy failed to detect signs of fungal infection.

The fifth patient with proven IFD was admitted at the age of 23 days for surgical treatment of pulmonary atresia with ventricular septal defect. He weighed 3.1 kg and had been born at 38 gestational weeks with a birth weight of 2.7 kg. The routinely performed microbiology at admission indicated preoperative colonization with methicillin-resistant *Staphylococcus aureus* and *C. albicans*. After diagnostic catheterization, unifocalization with creation of aorto-pulmonary shunts made of Gore-tex® (3.5 mm in diameter) was performed bilaterally. The postoperative period was complicated by low cardiac output syndrome. Reoperation through the left thoracotomy 2 days after the first intervention due to shunt dysfunction was also necessary. On the 15th day after the first surgery, clinical examination revealed a painful erythematous and oedematous scrotum. However, fever was not detected. The white blood count, CRP and PCT levels were 11.16 g/l, 68 mg/l and 0.55 ng/ml, respectively. An examination of the scrotum by the consulting surgeon revealed mucopurulent tissue infiltration. Empirical therapy with meropenem, vancomycin and fluconazole was initiated. During the next 24 h, erythaema and oedema spread rapidly over the groin and the left side of the chest. Fournier's gangrene was diagnosed and emergency surgical debridement was performed. Tissue samples were taken for microbiological examination. All microbiological samples revealed the presence of *C. albicans*. Fluconazole was replaced by caspofungin and was administered intravenously for 14 days, followed by fluconazole. The outcome was good.

The 3 cases of proven candidaemia and the case with Fournier's gangrene were initially treated with caspofungin (Cancidas®) with a loading dose of 70 mg/m^2 followed by daily doses of 50 mg/m^2 thereafter. In 3 of these 4 patients, the antifungal treatment

(14, 20 and 30 days, respectively) was successful and did not have any adverse effects of antifungal therapy. Thus, caspofungin completely eradicated the fungal infection in these cases. The fourth patient, who had undergone ventricular septal defect closure and reoperation after 2 days, developed liver insufficiency during caspofungin treatment. Therefore, the standard dose of caspofungin treatment had to be reduced to 35 mg/m^2. After 3 days of this antifungal treatment, the child presented with symptoms of invasive fungal endocarditis and echocardiography revealed aorta–right atrium communication. At the same time, chest ultrasound examination and X-ray revealed signs of pulmonary fungal invasion. The patient did not undergo CT because of deterioration of his general state. Owing to the multiorgan IFD, caspofungin (35 mg/m^2) was combined with amphotericin B lipid complex (Abelcet®) at a dose of 5 mg/kg. After 11 days of this antifungal treatment, the signs and symptoms of the infection retreated and *Candida* could not be cultured from the blood.

All 5 children with IFD survived the 30-day postoperative period. When all 1540 cases of cardiac surgical interventions in paediatric patients were examined, the overall 30-day mortality was 2.08%. The child with rib fungal invasion died 39 days after the surgery as a result of multiorgan failure. The overall in-hospital mortality for the entire series was 2.76%. The 3 patients who developed proven candidaemia in the early postoperative period after cardiosurgery with ECC were still alive 19, 71 and 75 months later, respectively (mean, 4 years and 7 months). The patient with Fournier gangrene is also still alive 4 months after the first surgery. He is presently awaiting the next step of the cardiac surgical treatment for pulmonary atresia with ventricular septal disease.

The patient whose IFD could not be proved exhibited the same clinical deterioration during the postoperative period that was observed in the patients with proven candidaemia. This patient was a 2.5-year-old girl with hypoplastic right ventricle with pulmonary atresia. She was treated surgically with ECC with the Fontan operation. The girl was preterm and hypotrophic, had Rubinstein–Taybi syndrome and was treated with antacids. In the postoperative period, she developed low cardiac output syndrome that was complicated by chylothorax, pneumothorax and renal insufficiency that required peritoneal dialysis. She underwent prolonged tracheal intubation, central vascular catheterization, catecholamine treatment and antibiotic and antifungal (fluconazole) treatment. On the 14th day after surgery, her general health condition deteriorated. Her CRP level rose from 12 to 45 mg/l. The WBC did not change (32 g/l both days). The PCT levels rose slightly to 0.63 ng/ml. Her Candida score was 4 points (severe sepsis, total parenteral nutrition and surgical treatment). According to Leon *et al*. [5], this indicates a high probability of fungal infection. Three blood samples were taken and caspofungin treatment at the standard dose was provided. The general condition of the patient improved within 36 h, and her clinical signs and labour signs of infection subsided. Her blood samples remained negative for fungal growth. The subsequent 8 months of observation were uneventful.

DISCUSSION

Invasive fungal infections caused by a variety of fungal species are becoming an increasing problem worldwide. In particular, *Candida* species have become the seventh most common cause of nosocomial sepsis in children [8]. The rate of infections in children with congenital heart diseases after surgical treatment is poorly researched, but reported incidences range from 2.8 to 3.1%. In terms of fungal infections, their incidence in this paediatric population has been reported to range from 0.2 to 0.65% [1, 2, 9, 10]. However, the literature on bacterial and especially fungal infections in this group of patients is rather limited. In the case of fungal infections, the literature largely relates to case reports or small series. The literature suggests that the difficulties faced in diagnosing fungal infections, especially in children, may lead to underdiagnosis of this complication.

Of the fungal pathogens that have been reported to complicate surgical treatment of congenital heart diseases in children, *Candida* is the most common. In the past, *C. albicans* was the most common species. At present, however, non-albicans are more commonly detected. This may reflect the frequent administration of azoles in clinical practice [8, 11]. In a series of children who developed candidaemia after cardiac surgery, the aetiological agents in 54 and 42% were *C. parapsilosis* and *C. albicans*, respectively [12]. Notably, several studies suggest that the postoperative mortality of this specific group of patients with invasive fungal infection differs depending on the centres: mortality rates range from 36 to even 100% [1, 3]. This may reflect the spectrum of fungal species at each centre: a study showed that mortality rates for IFD in paediatric intensive care units were 8.5, 13.5 and 23.3% when the infection was with *C. albicans*, *C. parapsilosis* and *C. tropicalis*, respectively [11].

Cardiac surgery differs from other types of surgery largely because of the frequent use of cardiopulmonary bypass and hypothermia, the complexity of the treatments, the long operation times, the prolonged postoperative intensive care unit stays and the use of many invasive therapeutic procedures. These risk factors may elevate the incidence of fungal infections in this group of patients. Many surgically treated paediatric cardiac patients also have additional risk factors, including low cardiac output syndrome, central vascular catheterization, endotracheal intubation, prematurity, exposure to broad-spectrum antibiotics, parenteral nutrition, antacid administration and preoperative *Candida* colonization. In relation to the latter risk factor, the rates of preoperative *Candida* colonization in children with congenital heart disease range from 5 up to 29% [13]. Moreover, acute organ failure in the postoperative period is an independent risk factor for proven IFD [1]. Another risk factor for IFD is systemic inflammatory response syndrome (SIRS), which commonly develops in patients who undergo surgery with ECC [14]. This complex inflammatory reaction induces transient immunosuppression in surgically treated paediatric cardiac patients, which may increase the risk of hospital-acquired infection in this group [15]. The management of SIRS is a major challenge at present because it is necessary to control inflammation while preserving a level of inflammation that is sufficient for host defence. Another factor that significantly increases the risk of SIRS and therefore the risk of infections in surgically treated paediatric cardiac patients relates to the use of implantable prosthetic material, particularly homografts or xenografts. Another well-known risk factor for infections in general is primary immune deficiencies (e.g. DiGeorge syndrome), which often coexist with certain congenital heart diseases.

The lack of guidelines regarding the diagnosis of IFD in paediatric cardiac patients after heart surgery markedly complicates this diagnosis when compared with IFD diagnosis in other groups of children. In general, 3–7% of the blood infections in infants after cardiac surgery are caused by fungi [3, 16]. Two studies reported that in children in the intensive care unit after surgical treatment, the median time to onset of clinical symptoms of candidaemia is 19–24 days after admission [6, 12]. In our small group of patients, the median time was 11 days after surgery. This corresponds with

the study of Klingspor *et al*., who performed a prospective multicentre survey that was initiated by the European Confederation of Medical Mycology: the survey reported that the median time from admission of a surgical patient to the intensive care unit to the first positive blood culture for *Candida* is 12 days [17]. However, it should be emphasized that the usefulness of blood culture in diagnosing fungal infection is limited by its low sensitivity; other diagnostic techniques as PCR should be evaluated as an alternative [18]. This could explain the therapeutic success of echinocandin in one of our children who had negative blood cultures. This case also supports the notion that supplementary techniques such as the Candida score should be used to identify possible cases of fungal infection, as this will allow these patients to be treated without delay in an empirical fashion. Trends in biochemical inflammatory variables in the postoperative period can support a diagnosis of IFD. Typically, IFD is characterized by increased CRP and normal or minimally elevated PCT levels [19]. We also observed this in the present study. However, exact cut-off levels for these variables that indicate IFD with reasonable reliability have not yet been determined. In relation to serum PCT levels, these levels are crucial for diagnosing and monitoring bacterial infections, but they are less reliable for diagnosing fungal infections. However, a PCT cut-off threshold of >1.3 ng/ml could be helpful in ruling out a fungal bloodstream infection [20].

The recommendations for the treatment of fungal infections, especially for invasive candidiasis in children, are extrapolated from the studies performed on adults. However, studies that specifically examine the effect of complex disease–drug combinations in children after cardiac surgical treatment, especially in cases of hypothermia with ECC or extracorporeal membrane oxygenation support, are needed. The optimal rescue strategy for this group of patients with IFD should be a 'hit fast, hit hard' approach [21]. An essential step in the management of candidaemia is to remove the central venous catheter as early as possible, as this significantly reduces mortality [22]. Recent data suggest that echinocandins should be the first-line therapy in patients with candidaemia [17, 23]. Recommended options for empirical treatment in paediatric patients of all age groups include liposomal amphotericin B (1–3 mg/kg) and caspofungin (loading dose 70 mg/m^2/day, followed by 50 mg/m^2/day) [23]. All patients who had candidaemia in our department received caspofungin with this regimen. This induced complete eradication of the fungal infection. In one case, namely, the patient who developed multiorgan IFD after fungal endocarditis caused by *C. albicans* and suboptimal treatment with caspofungin due to liver insufficiency, we combined echinocandin with amphotericin B lipid complex, which had a good outcome. It is important to note that none of the children in our study developed complications that related directly to the antifungal treatment, and that all patients survived the early postoperative period.

In our opinion, in the face of the many risk factors for fungal infections in paediatric cardiac patients, it is essential to provide IFD prophylaxis. Fluconazole is recommended in all neonatal departments that may have significant incidences of IFD [21]. In addition, fluconazole prophylaxis is recommended routinely in older paediatric cardiac patients, especially those who are supported with extracorporeal membrane oxygenation [24]. However, it should be emphasized that fluconazole prophylaxis does not provide total protection from *Candida* infection. All *C. krusei* and many *C. glabrata* strains are resistant to fluconazole. Moreover, Klingspor *et al*. reported that 44% of 98 patients who developed invasive candidiasis despite receiving prophylactic fluconazole had *C. albicans*; the next most common species were *C. parapsilosis* (27.6%), *C. glabrata* (17.4%) and *C. krusei* (4.1%) [17]. It was recently reported that breakthrough fungal infections may be the result of underdosing antifungal treatment. We consider fluconazole prophylaxis at a dose of 3–6 mg/kg/dose twice weekly to be insufficient for paediatric cardiac surgery patients. However, to prevent invasive candidiasis in non-neutropaenic paediatric patients in the intensive care unit, fluconazole 8–12 mg/kg/day administered intravenously or orally remains a reasonable option [23]. It is worth noting here that children on extracorporeal membrane oxygenation require a higher fluconazole loading dose for both prophylaxis (12 mg/kg) and treatment (35 mg/kg). This is because of the increased volume of distribution and decreased clearance [25]. In our department, we start antifungal prophylaxis with fluconazole (8–12 mg/kg/day) on the second postoperative day if the patient meets certain risk factors, especially low postoperative cardiac output syndrome.

In conclusion, fungal infections in paediatric patients after cardiac surgery may radically influence morbidity and mortality. However, guidelines for both prophylaxis and treatment are lacking. Proper prophylaxis of fungal infections in this specific group of patients may reduce morbidity. Early empirical treatment followed by a targeted approach may also improve outcomes. We recommend that IFD in paediatric cardiac patients should be tackled by a comprehensive strategy that includes a thorough analysis of several key risk factors, namely, the Candida score, preoperative *Candida* colonization status and biochemical marker trends. Moreover, early and proper antifungal prophylaxis and treatment with combined multidrug therapy is needed. The strategy of 'hit fast, hit hard' may be the best rescue option for children who develop IFD after cardiac surgery.

Conflict of interest: Radoslaw Jaworski and Ninela Irga-Jaworska have received personal fee for lecture from MSD Polska.

REFERENCES

[1] Forstner C, Lassnigg A, Tobudic S, Schiferer A, Fischer H, Graninger W *et al*. A prospective analysis of invasive candidiasis following cardiac surgery: severity markers are predictive. J Infect 2013;66:528–35.
[2] Kansy A, Jacobs JP, Pastuszko A, Mirkowicz-Malek M, Manowska M, Jezierska E *et al*. Major infection after pediatric cardiac surgery: external validation of risk estimation model. Ann Thorac Surg 2012;94:2091–5.
[3] Abou ER, Najm HK, Balkhy H, Bullard L, Kabbani MS. Impact of bloodstream infection on the outcome of children undergoing cardiac surgery. Pediatr Cardiol 2010;31:483–9.
[4] De PB, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T *et al*. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813–21.
[5] Leon C, Ruiz-Santana S, Saavedra P, Galvan B, Blanco A, Castro C *et al*. Usefulness of the 'Candida score' for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. Crit Care Med 2009;37:1624–33.
[6] Chakrabarti C, Sood SK, Parnell V, Rubin LG. Prolonged candidemia in infants following surgery for congenital heart disease. Infect Control Hosp Epidemiol 2003;24:753–7.
[7] Garcia-San ML, Cobo J, Martos I, Otheo E, Muriel A, Pintado V *et al*. Risk factors for candidemia in pediatric patients with congenital heart disease. Infect Control Hosp Epidemiol 2006;27:576–80.
[8] Kumar D, Kumar A, Singh S, Tilak R. Candidemia-induced pediatric sepsis and its association with free radicals, nitric oxide, and cytokine level in host. J Crit Care 2015;30:296–303.

[9] Cox EG, Knoderer CA, Jennings A, Brown JW, Rodefeld MD, Walker SG *et al*. A randomized, controlled trial of catheter-related infectious event rates using antibiotic-impregnated catheters versus conventional catheters in pediatric cardiovascular surgery patients. J Pediatric Infect Dis Soc 2013;2:67–70.
[10] Jaworski R, Irga N, Haponiuk I, Chojnicki M, Arlukowicz E, Steffek M *et al*. Candidemia in children after complex congenital heart defects surgery treated with caspofungin—our own experience and a review of literature. Med Sci Monit 2011;17:H35–9.
[11] Jordan I, Hernandez L, Balaguer M, Lopez-Castilla JD, Casanueva L, Shuffelman C *et al*. *C. albicans*, *C. parapsilosis* and *C. tropicalis* invasive infections in the PICU: clinical features, prognosis and mortality. Rev Esp Quimioter 2014;27:56–62.
[12] San Miguel LG, Cobo J, Otheo E, Martos I, Muriel A, Fortun J *et al*. Candidemia in pediatric patients with congenital heart disease. Diagn Microbiol Infect Dis 2006;55:203–7.
[13] Lex DJ, Toth R, Cserep Z, Breuer T, Sapi E, Szatmari A *et al*. Postoperative differences between colonization and infection after pediatric cardiac surgery—a propensity matched analysis. J Cardiothorac Surg 2013;8:166.
[14] Jaworski R, Haponiuk I, Irga-Jaworska N, Chojnicki M, Steffens M, Szofer-Sendrowska A *et al*. Kinetics of C-reactive protein in children with congenital heart diseases in the early period after cardiosurgical treatment with extracorporeal circulation. Adv Med Sci 2014;59:19–22.
[15] Axelrod DM, Alten JA, Berger JT, Hall MW, Thiagarajan R, Bronicki RA. Immunologic and infectious diseases in pediatric cardiac critical care: proceedings of the 10th international pediatric cardiac intensive care society conference. World J Pediatr Congenit Heart Surg 2015;6:575–87.
[16] Murray MT, Krishnamurthy G, Corda R, Turcotte RF, Jia H, Bacha E *et al*. Surgical site infections and bloodstream infections in infants after cardiac surgery. J Thorac Cardiovasc Surg 2014;148:259–65.
[17] Klingspor L, Tortorano AM, Peman J, Willinger B, Hamal P, Sendid B *et al*. Invasive *Candida* infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006–2008). Clin Microbiol Infect 2015;21:87.
[18] Taira CL, Okay TS, Delgado AF, Ceccon ME, de Almeida MT, Del Negro GM. A multiplex nested PCR for the detection and identification of *Candida* species in blood samples of critically ill pediatric patients. BMC Infect Dis 2014;14:406.
[19] Marková M, Brodská H, Malíčková K, Válková V, Cetkovský P, Kolář M *et al*. Substantially elevated C-reactive protein (CRP), together with low levels of procalcitonin (PCT), contributes to diagnosis of fungal infection in immunocompromised patients. Support Care Cancer 2013;21:2733–42.
[20] Leli C, Ferranti M, Moretti A, Al Dhahab ZS, Cenci E, Mencacci A. Procalcitonin levels in gram-positive, gram-negative, and fungal bloodstream infections. Dis Markers 2015;2015:701480.
[21] Manzoni P, Mostert M, Castagnola E. Update on the management of *Candida* infections in preterm neonates. Arch Dis Child Fetal Neonatal Ed 2015;100:F454–9.
[22] Karadag-Oncel E, Kara A, Ozsurekci Y, Arikan-Akdagli S, Cengiz AB, Ceyhan M *et al*. Candidaemia in a pediatric centre and importance of central venous catheter removal. Mycoses 2015;58:140–8.
[23] Hope WW, Castagnola E, Groll AH, Roilides E, Akova M, Arendrup MC *et al*. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp. Clin Microbiol Infect 2012;18 (Suppl 7):38–52.
[24] Gardner AH, Prodhan P, Stovall SH, Gossett JM, Stern JE, Wilson CD *et al*. Fungal infections and antifungal prophylaxis in pediatric cardiac extracorporeal life support. J Thorac Cardiovasc Surg 2012;143:689–95.
[25] Watt KM, Gonzalez D, Benjamin DK Jr, Brouwer KL, Wade KC, Capparelli E *et al*. Fluconazole population pharmacokinetics and dosing for prevention and treatment of invasive Candidiasis in children supported with extracorporeal membrane oxygenation. Antimicrob Agents Chemother 2015;59:3935–43.