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Swiss Evaluation Registry for Pediatric Infective Endocarditis (SERPIE) - Risk factors for complications in children and adolescents with infective endocarditis

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ABSTRACT

Background: Infective endocarditis (IE) in pediatric patients is a severe cardiac disease and its actual epidemiology and clinical outcome in Switzerland is scarcely studied.
Methods: Retrospective nationwide multicenter data analysis of pediatric IE in children (<18 years) between 2011 and 2020.
Results: 69 patients were treated for definite (40/69;58%) or possible IE (29/69;42%). 61% (42/69) were male. Diagnosis was made at median 6.4 years (IQR 0.8–12.6) of age with 19 patients (28%) during the first year of life. 84% (58/69) had congenital heart defects. IE was located on pulmonary (25/69;35%), mitral (10/69;14%), tricuspid (8/69;12%) and aortic valve (6/69;9%), and rarely on ventricular septal defect (VSD;4/69;6%) and atrial septal defect (ASD;1/69;1%). In 22% (16/69) localization was unknown. 70% (48/69) had postoperative IE, with prosthetic material involved in 60% (29/48; right ventricular to pulmonary artery conduit (24), VSD (4), ASD (1)). Causative organisms were mostly *Staphylococci spp.* (25;36%) including *Staphylococcus aureus* (19;28%), and *Streptococci spp.* (13;19%). 51% (35/69) suffered from severe complications including congestive heart failure (16;23%), sepsis (17;25%) and embolism (19;28%). *Staphylococcus aureus* was found as a predictor of severe complications in univariate and multivariate analysis ($p = 0.02$ and $p = 0.033$). In 46% (32/69) cardiac surgery was performed. 7% (5/69) died.
Conclusions: IE in childhood remains a severe cardiac disease with relevant mortality. The high morbidity and high rate of complications is associated with *Staphylococcus aureus* infections. Congenital heart defects act as a risk factor for IE, in particular the high number of cases associated with prosthetic pulmonary valve needs further evaluation and therapeutic alternatives.

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1. Introduction

Infective endocarditis (IE) in childhood is associated with high morbidity and mortality [1–3]. The incidence of pediatric IE is reported with 0.43–0.84/100′000 children per year [4–7], with increasing trend in recent years [8–11].

In developed countries, congenital heart disease (CHD) plays the dominant role as predisposing factor for pediatric IE [4,6,7,12–14]. This includes children with native and prosthetic valves affected [1,10,15]. Nowadays, prosthetic valve IE in children with CHD are associated with severe clinical course leading to complications [13,15]. From the clinical point of view, early determination of risk factors contributing to complications is essential.

Due to the limited cases of pediatric IE, multicenter surveys such as nation-wide registries are needed. In Switzerland, two single-center studies on pediatric infective endocarditis have been published [16,17]. So far, nation-wide data are missing. Therefore, the *Swiss Evaluation Registry for Pediatric Infective Endocarditis* (*SERPIE*) was founded in 2020 with the purpose to build up a prospective data collection of the microbiological spectrum, diagnostics, predisposing risk factors, clinical course, complications, therapy, and outcome of pediatric IE in Switzerland. To optimally prepare for the launch of the *SERPIE*, we conducted the analysis based on national retrospective data on pediatric IE presented here.

As it seems that especially children with CHD experience more severe courses of IE [13,15], and in the last two studies conducted in Switzerland, mainly children with CHD were found to be at risk for IE, especially when foreign material was used for treatment of the CHD [16,17], the *SERPIE* study also aimed to analyze factors associated with complicated clinical courses.

2. Methods

2.1. Study design

In 2020, a network of pediatric cardiologist and pediatric infectious disease specialists was built up on behalf of the *"Verein Kinderherzforschung Schweiz"* (*Association of Children's Heart Research Switzerland*) and with the consent of the participating pediatric cardiac surgeons and the Swiss Society of Pediatric Cardiology. In Switzerland, the pediatric cardiac surgery program concentrates on four main tertiary pediatric heart centers performing invasive pediatric cardiac procedures including cardiac surgery as well as catheter-based cardiac interventions. This includes the tertiary Pediatric University Children's Hospital in Berne, Geneva, Lausanne, and Zurich.

This study was designed as a retrospective nationwide multicenter analysis including cases of pediatric infective endocarditis in children under 18 years of age treated in Switzerland between 2011 and 2020. After ethical committee approval was achieved (BASEC Number 2021–00862), patients were searched in the local medical data bases in each of the main four pediatric cardiac center, since our preliminary discussion revealed that all cases treated for IE have been doubtfully treated within these four main centers or in direct cooperation with them.

2.2. Patients and variables

Patients' consent was given by primary (general) consent for retrospective data analysis, or a secondary consent was obtained in written form for study participation. Only patients fulfilling the modified Duke criteria for definite or possible IE were included [18]. Patients' data were recorded in an encoded way into REDCap®. We collected data analysis regarding diagnostic, microbiological, clinical and therapeutic variables, and outcomes. To calculate the incidence of IE in Switzerland, national data from the Federal Statistical Office on children under 18 years of age living in Switzerland were used (https://www.bfs.admin.ch/bfs/de/home/stastiken/bevoelkerung/stand-entwicklung/bevoelkerung.assetdetail.18404679.html).

Based on the AHA guideline for the antibiotic endocarditis prophylaxis from 2007 [19], which were adopted in 2008 for Switzerland [20], all patients were classified into a "predisposed" or "non-predisposed" group, *i.e.* antibiotic prophylaxis was recommended or not during high-risk interventions. This includes patients with prosthetic valve, patients with previous IE, patients with unrepaired cyanotic CHD including palliative shunts and conduits or patients with any type of CHD repaired with a prosthetic material within 6 months after procedure or lifelong if residual shunt remains [19]. The first day of intravenous antibiotic therapy was defined as the day of diagnosis of IE. Postoperative IE was diagnosed if the patient underwent previous cardiac surgery or catheter intervention. Severe complications were defined as sepsis, embolism or severe congestive heart failure [21]. Severe congestive heart failure was defined as impaired ventricular myocardial function determined by echocardiography, hemodynamic instability, and clinical signs of congestive heart failure such as hepatomegaly, pulmonary oedema, or cardiac-related renal failure. Patients were classified into "acute" *versus* "subacute" IE accordingly to their clinical course. IE was defined as "acute" if severe complications occurred and/or early surgical intervention during antibiotic treatment was performed. Predisposing factors for IE were known CHD, prior history of IE, comorbidities like immunodeficiency, genetic or oncologic comorbidities, and temporary or permanent inserted central venous catheter line before diagnosis of IE.

2.3. Statistics

Statistical analysis was performed using STATA Version 16 (StataCorp, Texas, United States of America). Continuous variables are described as medians and interquartile ranges (IQRs), categorial variables as counts and frequencies. Yearly and median incidence was calculated using the yearly respective median numbers of patients treated for IE and children under 18 years of age living in Switzerland. Intergroup comparison was done using Kruskal-Wallis test for continuous variables and chi-square test or Fisher's exact test for categorial variables. A multivariate logistic regression analysis with adjustment for age, co-morbidities and gender was performed for each potential predictor identified in the univariate analyses (with P-value ≤ 0.05) and adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated. All tests were 2-tailed, and a P-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Patients

The medical data base research revealed a total number of 95 patients fulfilling inclusion criteria. 24 patients were treated as part of humanitarian project and lost to follow up. For 48 patients a primary consent was available. Of the remaining 23 patients, 2 refused consent so that finally a total of 69 patients were included in the study.

Patients fulfilled the modified Duke criteria for definite IE and for possible IE in 58% (40/69) and 42% (29/69) of cases, respectively. IE was diagnosed at a median age of 6.4 years (IQR 0.8–12.6) with 28% (19/69) during the first year of life. 61% (42/69) were male patients. The median incidence of IE was 0.33 (IQR 0.27–0.54) patients per year and 100′000 children under 18 years of age living in Switzerland.

3.2. Predisposing factors for IE

Fifty-eight of the 69 (84%) patients had a documented congenital heart disease (Table 1) as a predisposing factor, of those 55% were cyanotic CHD (32/58). 17% were unrepaired CHD (10/58), while 83% (48/58) patients had postoperative IE. At least 60% (29/48) of the patients with postoperative IE were proven to be associated with prosthetic

Table 1
Predisposing factors for IE in children.

Congenital heart disease*		RV-PA conduit
Cyanotic CHD	*n* = 32	*n* = 26
Tetralogy of Fallot (TOF)	n = 9	n = 9
Pulmonary atresia (PA)	n = 7	n = 7
Double outlet right ventricle (DORV)	n = 5	n = 3
Truncus arteriosus communis	n = 4	n = 4
Transposition of the great arteries (TGA)	*n* = 3	*n* = 2
Hypoplastic left heart syndrome (HLHS)	*n* = 2	n = 1
Double outlet right ventricle with tricuspid atresia (DORV +TA)	*n* = 1	*n* = 0
Unbalanced AVSD	*n* = 1	*n* = 0
Non-cyanotic CHD	n = 26	n = 6
Ventricular septal defect (VSD)	n = 8	n = 0
Bicuspid aortic valve (AV)	n = 6	n = 2
Atrioventricular septal defect (AVSD)	*n* = 4	n = 0
Aortic valve (AV) stenosis	n = 3	n = 2
Atrial septal defect (ASD)	*n* = 2	n = 0
Absent pulmonary valve (PV)	n = 1	n = 1
Shone-complex	*n* = 1	n = 1
Complete atrioventricular (AV)-block	n = 1	n = 0
Other predisposing factors*		
Central venous line	n = 9 (one permanent)	
Genetic syndromes	n = 5	
DiGeorge syndrome	n = 3 (one with trisomy 9p)	
Trisomy 21	*n* = 1	
Right isomerism with asplenia	*n* = 1	
Immunodeficiency	n = 4	
Hypogammaglobulinemia	n = 2	
Autoimmune neutropenia	n = 1	
Chronic granulomatous disease	*n* = 1	
Oncologic comorbidities	n = 3	
Common ALL	n = 2	
Kidney clear cell sarcoma	n = 1	
Preterm	n = 2	
Previous IE	n = 2	
No known predisposing factors	n = 8	

* some patients presented with more than one predisposing factor.

material. Postoperative IE was diagnosed at a median of 1.5 years (IQR 0.4–8.8) after cardiac intervention. Ten of 48 (21%) patients with postoperative IE had an early postoperative IE within 30 days after cardiac procedure. Two of the 69 (3%) patients already suffered from IE before. According to the guidelines for antibiotic prophylaxis in Switzerland, 61% (42/69) of the patients were at high risk for IE, where antibiotic prophylaxis is recommended [20]. In only 2 cases prior dental treatment was documented, these children received antibiotic prophylaxis.

In the group of patients with CHD, the following additional risk factors were found: central venous catheter (*n* = 6), genetic syndromes (*n* = 5), oncologic comorbidities (*n* = 3), primary immunodeficiency (*n* = 2) and previous IE (n = 2). Two patients with CHD were born preterm with persistent ductus arteriosus (PDA) and IE occurring early after birth.

In 29 of 69 (42%) a possible source for transient bacteremia was identified, mostly skin or soft tissue infections (*n* = 10), or central venous catheters (*n* = 9; see Table A in appendix).

3.3. Localization of IE

IE affected valves in pulmonary (25/69; 35%), mitral (10/69; 14%), tricuspid (8/69; 12%) and aortic position (6/69; 9%), VSD (4/69; 6%), ASD II (1/69; 1%) and PDA (2/69; 3%). Multiple infections occurred in 2 of 69 (3%) patients, with one patient with IE affecting tricuspid valve and a VSD-patch, and one patient with an unrepaired AVSD with infected mitral and tricuspid valve and infected PDA. Localization was undetermined in 16 of 69 (22%). In total, isolated right sided IE occurred in 31 of 69 (45%), isolated left sided IE in 15 of 69 (22%).

Prosthetic valve associated IE affected only the right ventricular to pulmonary artery (RV-PA) conduit in 24 of 48 (41%) postoperative IE. The type of RV-PA conduit affected included in 18 of 24 (75%) predominately the Contegra valve conduit (Medtronic Co., Münchenbuchsee. Switzerland), in 4 of 24 (17%) the Melody valve (Medtronic Co., Münchenbuchsee, Switzerland), in 1 of 24 (4%) a homograft, and in 1 of 24 (4%) a Shelhigh-Conduit (Shelhigh Inc., New Jersey, USA). Of note, all IE localized in a VSD or ASD were associated with foreign material such as VSD patches (*n* = 3) including a loose patch VSD, or Amplatzer (Abbott Medical Co., Baar, Switzerland) septal occluder for VSD (*n* = 1) or ASD (n = 1) closure. All 16 of 69 (22%) patients with undetermined localization of IE had CHD, the majority (13/16; 81%) had postoperative IE with implanted foreign material in 12 of 13 (92%) patients. Implanted foreign material in these patients included VSD patch (*n* = 10), RV-PA (*n* = 7, Contegra valve (*n* = 5), Melody valve (*n* = 2)), prosthetic mitral valve, ASD patch or other (each n = 1).

3.4. Imaging findings

In all patients (69/69; 100%) transthoracic echo (TTE) was performed for diagnosis, 29% (20/69) additionally underwent transesophageal echo (TEE). Positive echocardiographic findings according to the Duke criteria were found in 42 of 69 (61%) patients including vegetation (38/42; 90%), new valve regurgitation (8/42; 19%), new dehiscence of prosthesis (2/42; 5%), and paravalvular abscess (2/42; 5%; multiple findings included). In 10 of 69 patients (14%) only pathologic echo findings not fulfilling the Duke criteria were found, in 17 of 69 patients (25%) echo was negative. Therefore, the positive rate according to Duke was 55% (38/69) in TTE and 60% (12/20) in TEE. With all pathologic findings included the positive rate was 71% (49/69) in TTE and 70% (14/20) in TEE.

One patient with negative echo presented the picture of IE on the pulmonary valve in PET-CT that was performed to ensure diagnosis.

3.5. Microbiological findings

Pathogens determined in blood culture are listed in Table 2. Blood culture negative IE was found in 8 of 69 (12%) patients. In 3 of 8 (38%) patients the causative pathogen could be determined by positive serology for *Coxiella burnetii* (*n* = 1), positive culture for *coagulase negative Staphylococcus* on an explanted valve (*n* = 1) and positive culture for *Nocardia* on tracheal secretion in a patient with chronic granulomatous disease (*n* = 1). No pathogen could be determined by any technique in 5 of 69 (7%) patients, all of them meeting the Duke criteria for *possible* IE.

Associated bacterial findings with the same pathogen determined in blood culture were found in 18% (11/61) with positive cultures of cerebrospinal fluid (*n* = 3), explanted valve material (*n* = 7), wound swab of necrotizing fasciitis (n = 1) and urine (n = 1).

3.6. Clinical findings and complications

Clinical findings are shown in Table 3. The diagnosis was made at median 6.5 days (IQR 3–14) after first symptom, which most often was fever (59/69; 86%). 58% (40/69) of the patients were diagnosed with acute IE.

One of the 69 patients (1%) did have no symptoms. This was a 3-month-old boy with complete congenital AV-blockage after implantation of a pacemaker with ventricular pacing leads. At echocardiographic follow-up 30 days after intervention, he presented with new tricuspid valve stenosis and pacemaker leads suspicious of infection. *Coagulase negative Staphylococcus* was identified on the replaced tricuspid valve.

Infectious diseases associated with the manifestation of IE were

Table 2
Blood culture findings.

	All patients $n = 69$ (100%)	Foreign material associated IE $n = 33$ (48%)	Non foreign material IE $n = 20$ (29%)	Unknown localization $n = 16$ (23%)
Staphylococcus spp.	$n = 25$ (36%)	$n = 10$ (14%)	$n = 11$ (16%)	n = 4 (6%)
Staphylococcus aureus	$n = 19$ (28%)	n = 7 (10%)	$n = 9$ (13%)	n = 3 (4%)
Coagulase negative Staphylococcus	n = 6 (9%)	n = 3 (4%)	n = 2 (3%)	n = 1 (1%)
Streptococcus spp.	n = 13 (19%)	n = 6 (9%)	n = 3 (4%)	n = 4 (6%)
Viridans-Streptococci	n = 10 (14%)	$n = 6$ (9%)	n = 0 (0%)	$n = 4$ (6%)
Non-Viridans-Streptococci	n = 3 (4%)	n = 0 (0%)	$n = 3$ (4%)	n = 0 (0%)
Enterococci spp.	n = 8 (12%)	n = 2 (3%)	n = 2 (3%)	n = 4 (6%)
HACEK	n = 6 (9%)	n = 2 (3%)	n = 2 (3%)	n = 2 (3%)
Other pathogens	n = 9 (13%)	n = 4 (6%)	n = 3 (4%)	n = 2 (3%)
Hemophilus influenza type B	n = 2	n = 0	n = 1	n = 1
Granulicatella adiacens	n = 2	n = 1	n = 0	n = 1
Abiotrophia defectiva	n = 1	n = 1	n =0	n = 0
E. coli	n = 1	n = 1	n = 0	n = 0
Klebsiella oxytoca	n = 1	n = 0	n = 1	n = 0
Serratia marescens	n = 1	n = 0	n = 1	n = 0
Candida albicans	n = 1	n = 1	n = 0	n = 0
Blood-culture negative IE	n = 8 (12%)	n = 5 (7%)	n = 3 (4%)	n = 0 (0%)

Abbreviations: HACEK = *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella.*

found in 20% (14/69) of patients, most often pneumonia (11/69; 16%) and meningitis (3/69; 4%; see Table B in appendix). Many children already presented with multiple infectious foci at the start of hospitalization, so it is not possible to say with certainty which one appeared first. 3 of the 69 patients (4%) suffered severe invasive infections: one immunocompetent patient had invasive Candida infection with pneumonia, a patient with hypogammaglobulinemia had invasive *Hemophilus influenzae* type B infection with epiglottitis, and one patient with chronic granulomatous disease suffered from systemic nocardiosis with septic shock and acute respiratory distress syndrome (ARDS).

3.7. Clinical course, therapy and outcome

Information on severe complications, therapy and outcome are listed in Table 3 (more detailed information in Table C in appendix). Intravenous specific antibiotic therapy (69/69; 100%) was performed for at least 4 weeks according to international guidelines [22]. Pathogens found in patients who required surgical intervention (Table 3) were *Staphylococcus spp.* (15/32; 47%), *Streptococcus spp.* (5/32; 16%), HACEK (3/32; 9%), Enterococcus (3/32; 9%) and other (4/32; 13%). Severe complications occurred in 52% (Table 3), 7% of patients (5/69) died.

A 2-month-old preterm infant (gestational age 33 6/7) died within 10 days after valve replacement due to severe congenital mitral valve regurgitation. He suffered IE of unknown localization and died of *coagulase-negative staphylococcal* sepsis with severe heart failure and cardiogenic shock.

A 17-year-old patient with DiGeorge syndrome and low native T

Table 3
Clinics, complications, therapy and outcome.

Clinical findings	
Fever and/or shivering	$n = 66$ (96%)
Decreased general health condition	n = 36 (52%)
New / altered valve function*	n = 29 (42%)
Aortic valve regurgitation	n = 5
Mitral valve regurgitation	n = 10
Mitral valve stenosis	n = 1
Pulmonary valve regurgitation	n = 4
Pulmonary valve stenosis	$n = 10$
Acute obstruction of melody valve	n = 1
Tricuspid valve regurgitation	n = 3
Tricuspid valve stenosis	n = 1
Gastrointestinal symptoms*	$n = 24$ (35%)
Nausea and/or vomiting	$n = 17$
Inappetence	n = 10
Diarrhea	$n = 13$
Abdominal pain	n = 8
Respiratory tract infection */**	n = 8 (12%)
Cough	n = 4
Dyspnea	n = 2
Rhinitis	n = 2
Sore throat	n = 2
IE specific skin affection*	n = 2 (3%)
Osler nodes	n = 2
Splinter hemorrhages	n = 2
Janeway lesions	n = 1
Unspecific skin affection*	n = 7 (10%)
Maculopapular exanthema	n = 3
Petechia	n = 3
Suffusion on left hand	n = 1
Other symptoms*	n = 19 (28%)
Headache	n = 11
Weight loss	n = 6
Myalgia / arthralgia	$n = 5$
No symptoms	n = 1 (1%)
Severe complications	
Congestive heart failure	n = 16 (23%)
Sepsis	n = 17 (25%)
Embolism	n = 19 (28%)
Lung	n = 11
Brain	n = 9
Spleen	n = 3
Kidney	n = 2
Extremities	n = 2
Retina	n = 1
Death	n = 5 (7%)
Surgical intervention	
Surgery done	n = 32 (46%)
Early surgical intervention needed	24/32 (75%)
Interval surgery after diagnosis IE, median days (IQR)	21 (7–41)
For isolated left heart infections	7 (3–20)
For isolated right heart infections	31 (11–64)
Indication for surgery***	
Valve regurgitation	13/32 (41%)
Valve stenosis	12/32 (38%)
Embolism or large valvular vegetations	10/32 (31%)
Pseudoaneurysm due to rupture of ventriculo-prostetic suture	1/32 (3%)
Change of pacemaker leads	1/32 (3%)
AVSD-direct closure	1/32 (3%)
Loose VSD-patch	1/32 (3%)
Type of surgery****	
Valve replacement	15/32 (47%)
Valve reconstruction	12/32 (38%)
Large vegetation removal	9/32 (28%)
Thrombus removal in right ventricle	2/32 (6%)
VSD-Closure	2/32 (6%)
ASD-Closure	1/32 (3%)
Change of pacemaker leads	1/32 (3%)
Hospitalization	
Duration of hospitalization, median days (IQR)	42 (23–46)
Intensive care needed	n = 40 (58%)

* multiple findings possible.
** without impaired cardiac function.

*** some patients fulfilled more than one indication for surgery.
**** some patients received more than one type of surgery.

cells, postoperative pulmonary atresia with implantation of a Melody valve died of pulmonary valve IE positive for *Staphylococcus aureus*. He suffered fulminant sepsis with multi-organ failure and DIC.

Another 4-month-old with HLSH died three months after cardiac surgery due to a *coagulase-negative Staphylococcus* IE on the tricuspid valve. Although he underwent surgical intervention with valve repair because of severe tricuspid regurgitation, he died of sepsis with heart failure and severe hypoxemia.

A 4-year-old child died after aortic valve IE and systemic nocardiosis with septic shock and multiple organ failure. After IE diagnosis, he was diagnosed with previously unknown chronic granulomatous disease.

A 6-month-old patient with AVSD repair three months prior to diagnosis of IE at unknown location died of enterococcal sepsis following necrotizing enterocolitis with ARDS and renal failure.

In our study period one patient had a relapse of IE.

3.8. Predictors for IE with complications

In univariate analysis, *Staphylococcus aureus*-infections was found as a predictor of severe complications, whereas age, CHD, prosthetic material and CRP levels at admission were not associated with complicated clinical courses (Table 4). In the multivariate analysis adjusted for age, gender and risk factors, *Staphylococcus aureus*-infection was also found as a predictor of severe complications ($p = 0.033$, OR 4.079, 95%-CI 1.117–14.89).

Table 4
Univariate analysis - predictors of severe complications in children with IE.

	All IE	By Severe Complications		
	n = 69	Present $n = 35$ (51%)	Not Present $n = 34$ (49%)	p-value
Age, median years (IQR)	6.39 (0.81–12.60)	6.90 (0.6–14.3)	5.35 (0.8–11.4)	0.50
Male, n total (%)	42/69 (61%)	25/42 (60%)	17/42 (40%)	0.07
Diagnosis after first symptome, median days (IQR)	6.5 (3–14)	6 (3–14)	7 (3–13)	0.90
Risk factors, n total (%)	59/69 (86%)	27/59 (46%)	32/59 (54%)	0.08
Congenital heart disease	58/69 (84%)	27/58 (46%)	31/58 (54%)	0.19
Cyanotic heart disease	32/69 (46%)	13/32 (41%)	19/32 (59%)	0.12
CHD recommended for antibiotic prophylaxis	42/58 (72%)	18/42 (43%)	24/42 (57%)	0.37
Previous IE	2/69 (3%)	1/2 (50%)	1/2 (50%)	1
Central venous catheter	9/69 (13%)	4/9 (44%)	5/9 (56%)	0.73
Postoperative IE, n total (%)	48/69 (70%)	21/48 (44%)	27/48 (56%)	0.26
Foreign material used	44/48 (92%)	20/44 (45%)	24/44 (55%)	0.62
RV-PA conduit	32/69 (46%)	13/32 (41%)	19/32 (59%)	0.12
Surgery within 30 days before diagnosis	9/69 (19%)	3/9 (33%)	6/9 (67%)	0.31
Localization of IE, n total (%)				0.70
Left heart	15/69 (22%)	10/15 (66%)	5/15 (33%)	
Right heart	31/69 (45%)	14/31 (45%)	17/31 (55%)	
Other	23/69 (33%)	11/23 (48%)	12/23 (52%)	
Pathogen found, n total (%)				**0.02**
Staphylococcus aureus	19/69 (28%)	14/19 (74%)	5/19 (26%)	**0.02**
Coagulase negative *Staphylococcus*	7/69 (10%)	5/7 (71%)	2/7 (29%)	0.43
Streptococcus	13/69 (19%)	5/13 (38%)	8/13 (62%)	0.33
HACEK	6/69 (9%)	3/6 (50%)	3/6 (50%)	1
Enterococcus	8/69 (12%)	5/8 (63%)	3/8 (37%)	0.71
Clinical course				
CRP level at admission, median concentration (mg/l) (IQR)	75 (32–157.2)	101.5 (47–206)	55.6 (28–106)	0.11

Abbreviations: CRP = c-reactive protein; HACEK = Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella; RV-PA = Right-ventricular to pulmonary artery conduit.

4. Discussion

This study constitutes the first nationwide analysis of pediatric infective endocarditis in Switzerland and based on the findings of 69 patients treated for IE between 2011 and 2020. The incidence for pediatric IE of 0.33 per 100′000 per year was comparable to prior published single center cohorts [17]. In our cohort, more than half of the patients suffered from severe complications leading to a high demand for surgical treatment in 46%.

The most frequent pathogen causing IE in our study population was *S. aureus* (26%) followed by *Viridans Streptococci* (14%). The impact of both pathogen is well-known since decades as the causative pathogen for pediatric IE [4,6,7,23,24]. In recent decades, however, there has been a shift towards an increasing number of *S. aureus* associated IE [11]. A contributing factor is that *Viridans Streptococci* are most common in patients with underlying CHD, whereas *Staphylococcus* is increasingly found in the absence of predisposing CHD [6,25,26]. The latter group seems to have increased in the last decades [27]. Overall, the increasing prevalence of more "aggressive" pathogens seem to change the clinical picture with frequent complications and severe clinical course.

The overall mortality in our study population was 7% and is comparable with recently published results for pediatric IE, ranging between 3% and 24% [3,4,6,7,11–15,24–26,28–30]. Despite the mortality, high morbidity of IE may be determined by the occurrence of major complications in more than half (51%) of our study population. All our patients dying from pediatric IE suffered from severe complications. In contrast to other studies investigating severe courses of pediatric IE, but focusing more on embolic complications or death [6,14,28], we analyzed three main complications including sepsis, embolism, and severe congestive heart failure. Therefore, the high number of complicated courses in our study population may be overestimated.

In our study population, *S. aureus* was found as a risk factor for severe complicative course (Table 4), which has been described by other groups as risk factor not only for complicated courses, but also for death [6,28,30]. However, we could not find an association between *coagulase-negative Staphylococcus* (CoNS) infection and severe complications, although CoNS were identified as the causative agent in two of the five patients dying due to postoperative IE. Other studies already described CoNS as a risk factor for severe complications and death in pediatric IE with prosthetic valves [31] as well as for the adult population [32].

Nearly half of our study population (47%) needed early surgical intervention for IE during antibiotic treatment, which is comparable with literature ranging from 30 to 60% [3,4,7,12,13,23,25,28,30,33]. In 47% of our patients requiring surgical therapy (15/32), *Staphylococcus* were found as causative organisms. Other studies already found *Staphylococcus* infections more frequent in patients who require surgical treatment [28,31]. Additionally, these patients seem to need earlier surgical treatment [23,31]. In our study population, 75% of all surgically treated patients required early surgery during antibiotic treatment. This proportion is difficult to compare with the literature, as many surgical publications defined early surgery as surgical intervention within 3 to 7 days of diagnosis [23,28,34].

For the adult population with IE, CRP levels at admission were found

as predictive risk factor for in-hospital mortality, severe complications such as embolism or congestive heart failure, and need for early surgical intervention [35–37]. Although CRP levels at admission in patients with severe complications were twice as high compared to patients without severe complications, we could not determine CRP levels as a predictor of severe complications (Table 4).

In our study population 84% had CHD (Table 1), most of them were cyanotic (32/58; 55%) and acquired postoperative IE (48/58, 83%) with a high rate of prosthetic material infections (29/48; 60%). Other studies found CHD as the major predisposing factor for IE [3–7,12,14,25,28], with increasing numbers of CHD associated IE during the last decades [10]. Especially complex and cyanotic CHD seem to be at risk [4,10,13,28,29]. Also the incidence of postoperative IE was found to be increasing [11] with higher risk for IE within the first months post-operative as well as after use of foreign material [10,13]. The high percentage of patients with CHD could also be due to the fact that there is a higher level of suspicion for IE in patients with a predisposition. This is especially required for diagnosis in children with unspecific clinical symptoms. [38]

The RV-PA conduit was the most frequent localization for pediatric IE overall (35%). Pulmonary valve in pediatric IE is reported in the literature between 17 and 38%, mostly in association with postoperative IE in children with CHD [3,12,25,30]. Overall, RV-PA infections seemed to have increased in recent years. A systematic review describes the incidence of IE after Melody valve implantation between 3 and 14% [1]. Another systematic review found the incidence of IE in adult populations higher in bovine jugular vein grafts (BJV) than other types of RV-PA conduits (5.4% *vs.* 1.2%, $p < 0.0001$), but no difference was found between surgical (Contegra) or catheter-based implanted RV-PA BJV grafts (Melody). The BJV grafts may be more sensitive due to their specific tissue characteristics predisposing to bacterial adhesion, while the implantation method itself (surgery *vs.* catheter-based) does not alter the risk for IE, as we had pediatric cases in both [39].

As other foreign material associated IE, we found 4 patients after VSD respectively one patient after ASD closure, either due to infected VSD patches ($n = 3$) or infected Amplatzer devices ($n = 2$). This type of pediatric IE after VSD or ASD correction using Amplatzer devices has rarely been described in case reports [2]. Jalal et al. found incomplete endothelialization in two thirds of Amplatzer device related IE >6 months after implantation. This delayed or incomplete endothelialization increases the risk of delayed infection so that the authors discussed a prolongation of postoperative AB prophylaxis [40].

Interestingly, neither CHD nor foreign material was found to be a risk factor for severe courses in our study. This is in contrast to the findings of various other studies, which state that CHD, especially severe or cyanotic CHD, is associated with increased mortality [13,15,29]. Furthermore, prosthetic valves have already been described as a risk factor for death [31].

Comparable to some recent findings that 28 to 33% of children with IE have septic embolism [3,4,41], 28% of our study population suffered this severe complication. On the contrary, our rates of thromboembolic complications are higher than other reported numbers of 6% and 15% [6,14]. These lower values could be explained by the fact that in both studies only stroke was considered as a thromboembolic complication, whereas in our study thromboembolic complications beyond the central nervous system were also included. However, a long-term Canadian study conducted over a 30-year period found that 40% of children with IE had thromboembolic complications in the first decade of this century, with thromboembolic events associated with age over 3 years [28]. As the median age of the patients in our study was younger (6.4y compared to 12.3y) and also more than a quarter of the patients in our study population were younger than one year, this could partly explain the different findings. Furthermore, an American study of neurological complications in pediatric infective endocarditis found that more than one fifth of the patients with neurological complications were asymptomatic and only found incidentally on screening neuroimaging [42]. In our study patients were not systematically screened for thromboembolic complications. This could lead to an underestimation of the events.

The rate of congestive heart failure in our study population (23%) as a complication of IE is higher than the 12 to 15% reported [4,14]. The comparison with both studies should be taken with caution, as neither study describes a definition of heart failure.

Right-sided infections occurred in almost half of the patients (45%), which is comparable to results from Belgium [12]. In a multicenter registry in Spain, right-sided infections were found to be more common in children with CHD, with infections of the RV-PA being most frequent [3]. Additionally, IE in pulmonary valve position has been found to increase in patients with complex CHD [1,12,25]. On the other hand, several other studies presented smaller numbers of right-sided infections (15–33%) [3,4,7,14]. In these studies either a lower percentage of CHD was found to be a predisposing risk factor [3,4,7] or the reported CHD were less complex and mostly involved VSD [14].

In 16 of our patients (22%) localization was unknown, all had CHD pre-diagnosed, and of them 81% (13/16) had postoperative IE with implanted foreign material in 75% (12/16). In other studies, no localization of IE was found in 14–33% of the patients [4,7,13,33], most of them having inconclusive echo due to CHD with complex anatomy or the use of prosthetic material [7,33]. A study on IE in adults found no vegetation on echo after implantation of pulmonary valves in up to 50% of cases, even after TOE [43]. Thus, an estimated number of unknown locations can be assumed, with the RV-PA conduits probably being affected even more frequently.

In 2015 the European Society of Cardiology (ESC) included 18F-fluorodeoxyglucose (18F-FDG) PET-CT as a diagnostic criteria for infective endocarditis as an “important supplementary method for patients with suspected IE and diagnostic difficulties” [21], for example in patients with suspected prosthetic valve IE [1]. In one of our patients definite diagnosis could be made by a positive PET-CT after inconclusive echo findings.

The main limitations of this study are the retrospective approach and low statistical power due to the sample size. Therefore, further studies with larger numbers of patients are needed to identify risk factors. Although the study was conducted nationwide with the participation of the four major tertiary cardiac centers, 69 patients could be included in the study over the last ten years. As only tertiary hospitals participated in the study, there may be a bias towards more severe courses. To avoid this bias, the smaller pediatric cardiology centers in Switzerland were contacted before the start of the study, showing that the patients with IE were all treated in collaboration with the large centers. Nevertheless, some patients might not have been included in the study, for example because they were treated by adult specialists. It would also be interesting to compare our pediatric data with data from adults in Switzerland. Unfortunately, there does not exist such comparable data yet. Also, this is the first study to look at the combination of severe complications including sepsis, congestive heart failure and embolism, which makes it difficult to compare our findings with other studies and the comparisons done should be taken with caution.

5. Conclusion

IE is still a severe cardiac disease in childhood with relevant mortality. It is also associated with relevant morbidity, including high rates of severe complications associated with *Staphylococcus aureus* infections and often involvement of surgical intervention. Congenital heart diseases represent a risk factor for IE, in particular the high number of cases associated with prosthetic pulmonary valve needs further evaluation and therapeutic alternatives.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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Appendix A. Appendix

Table A
Possible transient bacteremia.

Possible transient bacteremia	$n = 29$ (42%)
Dental source	$n = 8$ (12%)
Carious tooth lesions	n = 2
Dental procedure before diagnosis	n = 4 (within 2 weeks to 2 months)
Gingivitis	$n = 1$
Aphthae	$n = 1$
Skin source	n = 10 (14%)
Sternotomy with wound infection	n = 1
Necrotizing fasciitis after *Varicella Zoster* infection	n = 1
Bacterial superinfection after *Herpes Zoster* infection	n = 1
Atopic dermatitis with excoriated lesions	n = 1
Laceration wound	n = 1
Abrasion wound	n = 1
Panaritium	n = 1
Cellulitis and folliculitis	n = 1
Acne	n = 1
Bee sting	n = 1
Central venous line	n = 9 (13%)
Temporary central venous line	n = 8
Permanent central venous line	n = 1
Other entry sites	n = 2 (3%)
Infectious sacroiliitis	$n = 1$
Scoliosis correction surgery	$n = 1$ (3 days before diagnosis)
Necrotizing enterocolitis	n = 1

Table B
Infectious diseases associated with manifested IE.

Associated infectious diseases*	$n = 14$ (20%)
Pneumonia	$n = 11$
Meningitis	n = 3
Osteomyelitis	n = 1
Epiglottitis	n = 1
Cholecystitis	n = 1
Pyelonephritis	n = 1
Polyarthritis	n = 1
Peritonitis after peritoneal dialysis due to heart-failure associated renal failure	n = 1

* multiple findings possible.

Table C
Cardiac and extracardiac findings and complications.

Cardiac findings and complications	$n = 36$ (52%)
Symptoms of heart failure***	$n = 16$ (23%)
Hemodynamic instability	n = 6
Pulmonary oedema due to left heart failure	n = 8
Hepatomegaly due to right heart failure	$n = 3$
Reduced myocardial function in echocardiogram	n = 2
Cardiac surgery associated complications	n = 2 (3%)
AV-Block grade II (Wenckebach) with hemodynamic instability	n = 1
Pericardial tamponade	$n = 1$
Other	n = 1 (1%)
Aneurysmatic RV-PA conduit	$n = 1$
Extracardiac findings and complications	
Neurologic complications*	$n = 11$ (16%)
Embolism	n = 9
Intracranial bleeding (2× combined with cerebral embolism)	n = 3
Status epilepticus	$n = 1$
Grand mal seizure (complex fever seizure)	n = 1
Renal complications*	n = 20 (29%)
Kidney injury / renal failure	n = 11

(*continued on next page*)

Table C (*continued*)

Cardiac findings and complications	$n = 36$ (52%)
Glomerulonephritis	$n = 15$
Renal embolism	$n = 2$
Pulmonal complications*	$n = 18$ (26%)
ARDS	n = 3
Embolism	n = 11
Pulmonary oedema	n = 8
Pulmonary hemorrhages	n = 1
Gastrointestinal complications*	n = 14 (20%)
Hepatomegaly due to right heart failure	n = 3
Shock liver	n = 1
Splenomegaly	$n = 8$
Splenic embolism	n = 3
Hematologic complications*	$n = 61$ (88%)
Anemia	$n = 58$
Thrombocytopenia (1× with purpura fulminans)	$n = 40$
Allergic complications	n = 2 (3%)
Type I allergic reaction to Penicillin	n = 1
Potential Stevens-Johnson-Syndrome due to Vancomycin	n = 1
Endocrinological complications	n = 2 (3%)
Infection-triggered SIADH	n = 1
Stress induced hyperglycemia	n = 1
Other complications	n = 5 (7%)
Rhabdomyolysis	n = 1
Vasculitis	n = 1
Conjunctival bleeding	n = 1
Retinal embolism	n = 1
Embolism into extremities	n = 1

Abbreviations: AV = atrio-ventricular; RV-PA = right ventricular to pulmonary artery; ARDS = acute respiratory distress syndrome; SIADH = syndrome of inadequate ADH-secretion.

* multiple findings possible.

** without impaired cardiac function.

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