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REVIEW

Infective endocarditis in congenital heart disease

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Abstract Congenital heart disease (CHD) has become the leading risk factor for pediatric infective endocarditis (IE) in developed countries after the decline of rheumatic heart disease. Advances in catheter- and surgery-based cardiac interventions have rendered almost all types of CHD amenable to complete correction or at least palliation. Patient survival has increased, and a new patient population, referred to as adult CHD (ACHD) patients, has emerged. Implanted prosthetic material paves the way for cardiovascular device-related infections, but studies on the management of CHD-associated IE in the era of cardiovascular devices are scarce. The types of heart malformation (unrepaired, repaired, palliated) substantially differ in their lifetime risks for IE. Streptococci and staphylococci are the predominant pathogens. Right-sided IE is more frequently seen in patients with CHD. Relevant comorbidity caused by cardiac and extracardiac episode-related complications is high. Transesophageal echocardiography is recommended for more precise visualization of vegetations, especially in complex type of CHD in ACHD patients. Antimicrobial therapy and surgical management of IE remain challenging, but outcome of CHD-associated IE from the neonate to the adult is better than in other forms of IE. *Conclusion:* Primary prevention of IE is vital and includes good dental health and skin hygiene; antibiotic prophylaxis is indicated only in high-risk patients undergoing oral mucosal procedures.

Keywords Infective endocarditis · Congenital heart disease · Cardiac surgery · Interventional cardiology · Echocardiography · Blood culture

Abbreviations

ACHD	Adult with congenital heart disease
AHA	American Heart Association
ASD	Atrial septal defect
ASDOS	Atrial septal defect occlusion system
AV	Aortic valve
CHD	Congenital heart disease
CHF	Congestive heart failure
CI	Confidence interval
CoA	Coarctation of the aortic arch
ESC	European Society of Cardiology
HACEK	*Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*
HLHS	Hypoplastic left heart syndrome
IE	Infective endocarditis
IVDA	Intravenous drug abuser
LA	Left atrium
LPA	Left pulmonary artery
LV	Left ventricle
MV	Mitral valve
NBTE	Nonbacterial thrombotic endocarditis

This work is dedicated to the memory of Professor Urs Bauersfeld (1956–2010).

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n.d.	No data
PA	Pulmonary artery
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
Pst	Pulmonary valve stenosis
PV	Pulmonary valve
PVA	Perivalvular abscess
RA	Right atrium
RHD	Rheumatic heart disease
RV	Right ventricle
SAS	Subaortic stenosis
3rd gen	3rd generation
TEE	Transesophageal echocardiography
TTE	Transthoracic ecocardiography
TV	Tricuspid valve
VSD	Ventricular septal defect

Introduction

Congenital heart disease (CHD) has become largely manageable in developed countries in the last two decades, and a large number of children with CHD survived until adulthood [19]. They have a completely repaired or, at least, palliated CHD, and are referred to as adult CHD (ACHD) patients or as grown up with CHD patients [37]. Improved medical and surgical approaches and use of prosthetic materials made this possible. Nevertheless, prosthetic material increases the risk of associated infections, and infective endocarditis (IE) remains one of the most feared complications of CHD [46].

Here, we review the clinical entity of CHD-associated IE. Databases PubMed/Medline, EMBASE.com, and web of science were searched for English language articles with mesh terms "endocarditis" and "congenital heart disease," between 1960 and 2007. We considered articles reporting more than 25 IE cases and providing information on cardiac diagnoses or procedures performed. A systematic meta-analysis of data was not possible because studies published to date are underpowered and retrospective.

Epidemiology

The incidence of IE in adults varies between 1.5 and six cases per 100,000 persons per year [22]. Men are affected at least twice as often as women [77]. In 11% to 13%, an underlying CHD is found [125, 126]. In children, incidence of IE is considerably lower with 0.34 to 0.64 cases per 100,000 children per year [34, 43, 110] and male-to-female ratio is 1.2:1 [1, 8, 9, 20, 21, 33, 34, 38, 42, 47, 58, 65, 67, 68, 72, 74, 79, 83, 84, 88, 97, 99, 100, 107, 108, 110, 111, 116, 119, 122, 127, 137]. We reviewed 32 original articles reporting 2,361 IE episodes in 2,298 patients during an observation time of 43,426 patient-years [1, 8, 9, 20, 21, 33, 34, 38, 42, 47, 58, 65, 67, 68, 72, 74, 79, 83, 84, 88, 97, 99, 100, 107, 108, 110, 111, 116, 119, 122, 127, 137]. Reports originated from 15 countries and were retrospective single-center reviews except three multi-center studies [34, 65, 97]. Thirteen studies included ACHD patients (age >18 years) [9, 33, 34, 38, 65, 68, 72, 74, 83, 97, 122, 127, 137]. Figure 1 shows occurrence of IE between 1930 and 2004 in

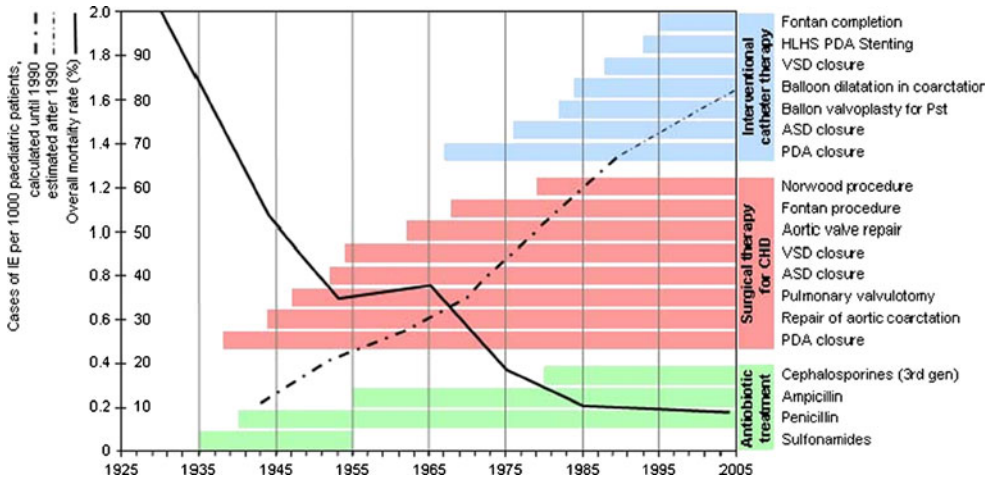

Fig. 1 Frequency and overall mortality of IE in CHD are shown in the context of the available antibiotic treatment and milestones of surgical and interventional catheter therapy. Mean values were compiled from retrospective clinical studies with at least 25 patients [1, 8, 9, 20, 21, 33, 34, 38, 42, 47, 53, 58, 65, 67–69, 72, 74, 79, 83, 84, 88, 97, 99, 100, 107, 108, 110, 111, 116, 119, 122, 127, 137]. *3rd* gen indicates 3rd generation, *ASD* atrial septal defect, *HLHS* hypoplastic left heart syndrome, *IE* infective endocarditis, *PDA* patent ductus arteriosus, *Pst* pulmonary valve stenosis, *VSD* ventricular septal defect

the context of milestones of antibiotic treatment, cardiac surgery, and interventional catheter therapy. Mean age at diagnosis of IE in pediatric patients was 10.3 years, with a bimodal age distribution with peaks during infancy and late teenage years [36]. Mean age of IE in ACHD patients ranged between 28 and 33 years, with a male-to-female ratio of 1.5 to 1 [38, 65, 97]. Around 4% of admissions to a ACHD-specialized unit were aimed for workup of IE, and recently, the frequency of adult-onset IE is 2.3% in ACHD patients [83, 128]. The proportion of nonvalvular cardiovascular device-related infections was as high as 5% [117].

Pathogenesis

CHD-associated IE results from complex interactions between valvular or mural endocardium and endothelium, blood components, circulating pathogens, and host defense mechanisms, similar to IE in structural heart disease [24]. The steps include (1) damage of valvular or mural endocardium, which exposes underlying matrix proteins to thromboplastin and tissue factors resulting in (2) development of nonbacterial thrombotic endocarditis (NBTE) following platelet and fibrin deposition, (3) microbial adherence to thrombi leading to (4) microbial colonization, invasion, and replication within lesions of thrombotic endocarditis, and (5) embolization of areas affected by microbial thrombotic endocarditis (Table 1).

Cyanosis in complex types of CHD before surgery and use of prosthetic material including palliative shunts, conduits, or other cardiovascular devices increase the IE risk [24, 134]. Mechanisms of cyanosis on the pathogenesis of IE are not clear.

Physical and chemical characteristics of prosthetic material, pathogen virulence factors, and host responses contribute to pathogenesis of (non)valvular cardiovascular device-related infections (Fig. 2) [11]. Prosthetic material with higher surface tension (polyethylene terephthalate) exhibits higher binding capacity for fibrinogen, a hydrated macromolecule [11], than material with lower surface tension (fluorocarbon polymers) and, thus, is more prone to initiate cardiovascular device-related infections. Key pathogenetic steps are binding of fibrinogen to prosthetic material and subsequent platelet aggregation. Pathogen factors include tissue and foreign body adherence molecules and foreign body surface biofilm formation [41]. Immediate host response to devices is mainly determined by induced alteration of intravascular/intracardiac laminar blood flow [115]. Shear stress of the endothelium by turbulent flow alters cell shape, changes cytoskeletal organization, and increases leukocytes and bacteria adhesion to the endothelium [76, 114, 115]. Notably, cardiovascular devices induce more chronic immune-mediated healing responses during endothelialization in the 6 months following implantation (Fig. 2) [5, 75].

Rheumatic heart disease (RHD) or CHD seem to be key for pathogenesis of IE in children. Nevertheless, in infants with intravascular catheters, NBTE de novo may contribute to affection of right-sided heart structures, similar to IE in intravenous drug abusers [95]. Epidemiologic studies on pediatric IE show a trend toward a higher proportion of children lacking pre-existing endocardial pathology in the past decade [36].

Predisposing risk factors

The type of heart malformation as the substrate of valvular, mural, or vascular damage and the source of bacteremia predispose for IE [24, 70, 134].

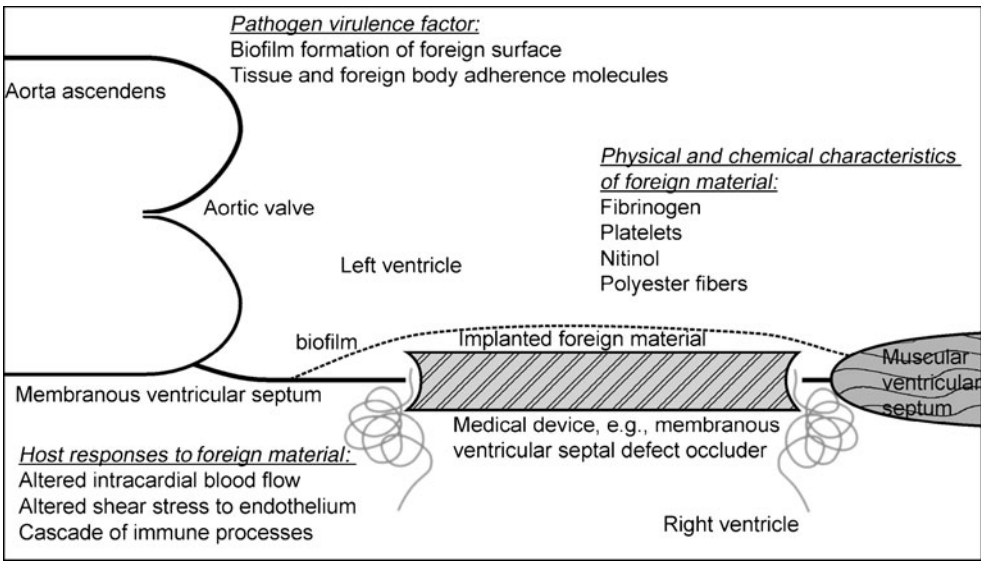

Fig. 2 Pathogenesis of cardiovascular device-related infections: catheter interventional closure of a membranous ventricular septal defect with a medical device as an example for foreign material

Type of heart malformation

Today, the incidence of RHD in industrialized countries is <10 per 100,000 children/year compared to up to 500 per 100,000 children/year in developing countries [27]. CHD became the major risk factor for IE in children in industrialized countries between 1950 and 1980, when RHD as predisposing factor decreased from 29% to <4% [1, 8, 9, 20, 21, 33, 34, 38, 42, 47, 58, 65, 67, 68, 72, 74, 79, 83, 84, 88, 97, 99, 100, 107, 108, 110, 111, 116, 119, 122, 127, 137].

The 2007 American Heart Association (AHA) guidelines regarding prevention of IE distinguish *unrepaired* CHD (with or without cyanosis), *repaired* CHD in biventricular malformations (with complete or incomplete repair with residual defects), and *palliated* CHD with functionally univentricular malformation (often by using prosthetic material) [134]. The lifetime risk for IE in unrepaired cyanotic CHD is up to 8.2 cases per 1,000 patients/year [32, 53] compared to the cumulative incidence of IE in repaired CHD during a 25-year follow-up after cardiac surgery of 0% after closure of secundum type atrial septal defect (ASD) to 13% after repair of aortic valve stenosis [96, 134]. Risk assessments of the three types of CHD for IE are hampered by simultaneous changes in the management of CHD (Fig. 1). Most types of CHD have become treatable either by repair or palliation. The number of unrepaired CHD decreased due to cardiac surgery or catheter-related cardiac interventions at younger age, whereas the number of complex type CHD palliated by Fontan procedure increased and patients may survive until adulthood (Fig. 1) [66].

Unrepaired CHD

Unrepaired cyanotic CHD associates with a higher lifetime risk for IE (8.2 cases per 1,000 patient-years) than unrepaired non-cyanotic CHD or repaired cyanotic CHD (ventricular septal defect 2.4 cases, repaired tetralogy of Fallot 2.3, aortic valve stenosis 2.0, or atrioventricular septal defect 1.7 per 1,000 patient-years) [32, 53]. The ratio of unrepaired cyanotic to non-cyanotic CHD of around 1:2 [65, 83, 108, 110, 111, 116] is comparable to that of cyanotic to non-cyanotic CHD in children [63].

Ventricular septal defect (VSD) is the most frequent CHD and, if unrepaired, the most frequent CHD associated with IE (Fig. 3) [83]. The incidence of IE in unrepaired VSD is 1.5 to 2.4 per 1,000 patient-years, especially if associated with aortic insufficiency or with left ventricle-to-right atrial shunt [32, 53]. For an ACHD patient with unrepaired VSD, the estimated lifetime risk for IE at age 30 years is 9.7% and by the end of life is 12% [52, 112]. In patent ductus arteriosus, atrioventricular septal defect, and ASD, IE is by far less frequent (Fig. 3). Whether complete closure of VSD is needed to control lifetime risk for IE requires careful individual risk–benefit analysis.

The second CHD most frequently associated with IE are outflow tract obstructions [83]. Estimated risks are 0.2% per 1,000 patient-years in native pulmonary stenosis compared to 1.8% in aortic valve stenosis [51, 52, 60]. Right ventricle outflow tract may be affected in malformations, such as tetralogy of Fallot, pulmonary atresia with or without VSD, and, less frequently, isolated pulmonary valve stenosis. The left ventricle may be affected in aortic valve diseases, including bicuspid aortic valve and coarctation of aortic arch (Fig. 3). Nevertheless, ACHD patients with left ventricular outflow tract obstructions seem to show a tendency toward developing IE more frequently than patients with VSD in the last two decades [52, 83]. This may be explained by the circumstance that residual hemodynamic lesions after surgery of left ventricular outflow tract obstructions are frequent, while complete closure of VSD may abolish the IE risk entirely [60, 134].

The anatomic location of IE in CHD differs from that in structural heart disease (Table 1) [1, 8, 9, 20, 21, 33, 34, 38, 42, 47, 53, 58, 65, 67–69, 72, 74, 79, 83, 84, 88, 97, 99, 107, 108, 110, 111, 116, 119, 122, 127, 137]. IE in CHD affects left heart structures (mitral valve>aortic valve) in around half of all cases (Fig. 3). The large proportion of affected right heart structures in CHD (one third of all cases) is the most striking difference compared to the structural heart disease (<5% of all cases). Notably, tricuspid valves are twice as frequently affected than pulmonary valves (Fig. 3). While valvular endocardium is predominantly involved in left-sided IE in patients with CHD, right-sided IE may also affect mural structures of the right ventricular wall such as surrounding VSD opening and at counterpoint VSD jet stream at the lateral wall [72]. Nevertheless, extracardiac structures including pulmonary artery, aortic arch, or systemic veins may also be involved in CHD patients [78]. The right heart is more prone to cardiovascular device-related infections than left heart [52, 96, 99], likely due to hemodynamic factors such as lower oxygen saturation or low pressure conditions (Table 2) [129].

Repaired CHD

Surgical or catheter interventional complete repair of CHD with sufficient endothelialization after 6 months may reduce risk for IE to that of healthy children, but the risk after incomplete repair with residual defects may not do so, [8, 33, 34, 38, 51, 53, 58, 60, 65, 69, 72, 79, 83, 84, 88, 97, 108, 119, 137]. The calculated ratio of post-interventional IE in repaired CHD (41%) compared to IE in unrepaired CHD (59%) is 2:3 [1, 8, 9, 20, 21, 33, 34, 38, 42, 47, 58,

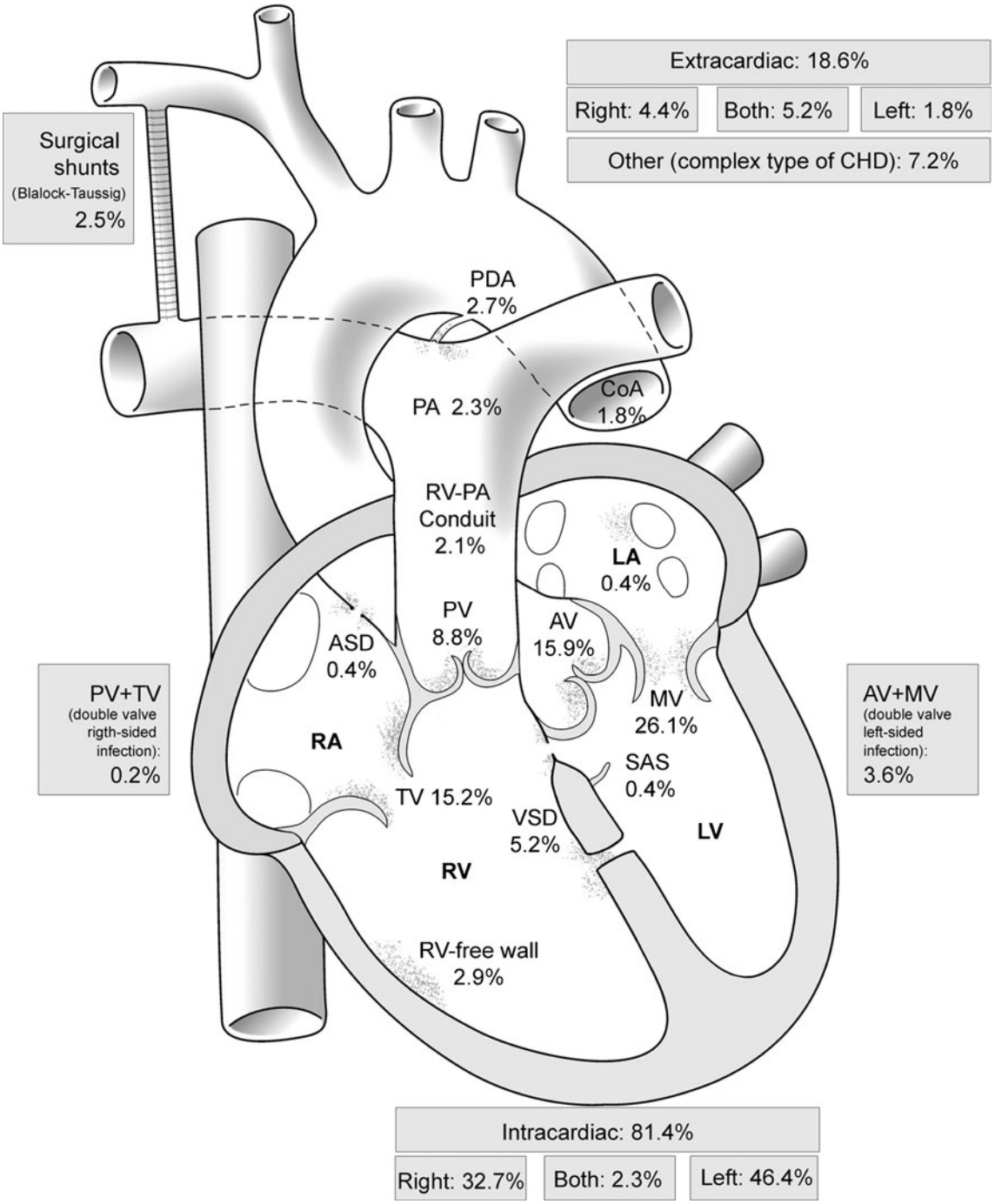

Fig. 3 Anatomic localization of infective endocarditis in congenital heart disease. Percentages of distribution of the different anatomic localization are calculated from the data of retrospective clinical studies [1, 8, 9, 20, 21, 33, 34, 38, 42, 47, 53, 58, 65, 67–69, 72, 74, 79, 83, 84, 88, 97, 99, 100, 107, 108, 110, 111, 116, 119, 122, 127, 137]. Extracardiac manifestations include shunts, conduits, and endarteritis in patent ductus arteriosus and coarctation of the aortic arch. *ASD* atrial septal defect, *AV* aortic valve, *CHD* congenital heart disease, *CoA* coarctation of the aortic arch, *MV* mitral valve, *LA* left atrium, *LV* left ventricle, *PDA* patent ductus arteriosus, *PV* pulmonary valve, *RA* right atrium, *RV* right ventricle, *SAS* subaortic stenosis, *TV* tricuspid valve, *VSD* ventricular septal defect

65, 67, 68, 72, 74, 79, 83, 84, 88, 97, 99, 100, 107, 108, 110, 111, 116, 119, 122, 127, 137]. Surgical complete repair may eliminate the IE risk [96], but implantation of prosthetic material may increase risk for post-interventional IE [117, 132]. Therefore, the cumulative incidence of IE within 25 years following cardiac surgery depends on the type of CHD: 0% for secundum type ASD, patent ductus arteriosus, and pulmonary valve stenosis;

Table 1 Synopsis of IE associated or not with congenital heart disease in children and adults

	Infective endocarditis not associated with congenital heart disease		Infective endocarditis associated with congenital heart disease	
	Child (<18 years)	Adult	Child (<18 years)	Adult
Pathogenesis	Native valve endocarditis [24]			
	Comparable pathogenetic steps: (1) damage of valvular or mural endocardium; (2) development of NBTE; (3) microbial adherence to NBTE; (4) microbial colonization, invasion, and replication within microbial thrombotic endocarditis; and (5) embolization of parts of microbial thrombotic endocarditis			
	Prosthetic valve endocarditis/cardiovascular device-related infection [11, 24]			
	Specific risk factors: (1) physical and chemical characteristics of foreign material [11], (2) pathogen virulence factors related to foreign material adherence [11], (3) host response to foreign material [114], (4) biofilm formation [41], and (5) endothelial dysfunction due to shear stress [5, 75, 115]			
	NTBE de novo [95]: in neonates with affection of right-sided normal heart structures [91, 93, 94, 101]	NTBE de novo [95]: in IVDA endocarditis	Specific risk factors [34, 46, 65, 88, 100, 108, 122]: (1) cyanotic heart disease; (2) palliative shunts, conduits, prosthesis; (3) age younger 2 years of age	Specific risk factors [65, 134]: foreign material such as palliative shunts, conduits, prosthesis
Pathogens	In healthcare-associated endocarditis [24, 35, 91] predominance of staphylococci, gram-negative bacteria, and fungi [123] In older children predominance of *S. aureus* [36]	*Streptococcus* spp. (40%) *Staphylococcus* spp. (40%)	*Streptococcus* spp. (42%) *Staphylococcus* spp. (26%)	*Streptococcus* spp. (46%) *Staphylococcus* spp. (28%)
		Others (*Enterococcus* spp., fungi, HACEK) (15%)	Others (*Enterococcus* spp., fungi, HACEK) (16%)	Others (*Enterococcus* spp., fungi, HACEK) (16%)
		Culture negative (5%) [24]	Culture negative (14%) [1, 8, 21, 24, 42, 47, 53, 58, 67–69, 84, 88, 99, 108, 110, 111, 116, 119]	Culture negative (10%) [9, 33, 34, 38, 65, 72, 74, 83, 97, 122, 127, 137]
Localization of lesions	Rheumatic heart disease [27, 70]: left-sided> right-sided mitral valve >aortic valve	Left-sided: mitral valve (40%)>aortic valve (25%)	Left-sided: mitral valve (26%) >aortic valve (16%)	Left-sided (60%): mitral valve >aortic valve [38, 65, 97]
		Right-sided: tricuspid valve (<10%), pulmonary valve (<5%), Other extracardiac (<5%) in IVDA (>50%) [24, 86]	Right-sided: tricuspid valve (15%), pulmonary valve (9%), other right-sided (14%), extracardiac struc tures (11%) [1, 38, 42, 65, 97, 111]	Right-sided (40%) [38, 65, 97]
Lifetime risk	Rheumatic heart disease [70]: risk of infective endocarditis 6%, females>males, mitral valve predominantly affected	Overall incidence: 1.5 to 6/100,000/year Elevated lifetime risk: (1) mitral valve prolaps (30%) in younger patients, (2) degenerative valvular disease (20%) in older patients, (3) hypertrophic cardiomyopathy (5%), (4) prosthetic valve (5–10%), and (5) intracardiac devices in IVDA: lifetime risk 1–5% [24]	Cyanotic (8.2/1,000 patients/ year)>non-cyanotic (1.7–2.4/ 1,000 patients/year) tetralogy of Fallot up to 25% postoperative risk for IE [32, 53]	Ventricular septal defect at an age of 30 years: 10% lifetime risk for IE. Adult IE is associated with CHD in 5% to 13% (bicuspid aortic valve in>20% of adults) [24, 43]
Episode-related complications	No data available	Cardiac: CHF (40%), PVA (35%), Extracardiac: emboli, overall (25%); cerebral (30%), renal (20%), peripheral affections (35%) [24]	Cardiac: CHF (30%), valvular damage (30%), PVA (<5%), arrhythmia (5%). Extracardiac: emboli, overall (20%); cerebral (15%), renal (10%), peripheral affections (<10%) [1, 8, 21, 24, 42, 47, 53, 58, 67–69, 84, 88, 99, 108, 110, 111, 116, 119]	Cardiac: CHF (25%), PVA (5–10%), arrhythmia (5%). Extracardiac: emboli, overall (20%), cerebral (10%), renal (5%), peripheral affections (<10%) [9, 33, 34, 38, 65, 72, 74, 83, 97, 122, 127, 137]
Outcome	No data available	Overall mortality (10–30%) [24] Surgical mortality (20%) [102] Recurrence (<10%) Early relapse (2–20%) Late relapse (1–10%)	Overall mortality (10%) [34, 65, 72, 79, 84, 97, 107, 135] Surgical mortality (14%) [34, 59, 72, 86, 97] Recurrence (<3%)	Overall mortality (10%) [65, 72, 135]

CHD congenital heart disease; *CHF* congestive heart failure; *HACEK Haemophilus* spp. *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*; *IVDA* intravenous drug abuse; *NBTE* nonbacterial thrombotic endocarditis; *PVA* paravalvular abscess

Table 2 Catheter-based procedures associated with infective endocarditis in children and adults with congenital heart disease

Author, year of publication/type of study	*N*=/age	Diagnosis	Device	Peri-interventional prophylaxis	Time interval procedure to diagnosis	Echocardiography	Microorganism	Antibiotic therapy	Surgery	Outcome
Slesnick et al., 2008/case report [118]	4 years	ASD II	Amplatzer septal occluder	n.d.	12 months	TTE: vegetation on device, TV, and MV	*Staphylococcus aureus*	Nafcillin+gentamicin for 6 weeks	Yes	Reoperation mitral valve repair 18 months later
Scheuerman et al., 2006/case report [109]	20 months	Muscular VSD	Amplatzer muscular occluder	Cefonicid	6 weeks	TTE: vegetation 10×12 mm LV side of device	*Kingella denitrificans*	Vancomycin+gentamicin, later cefuroxime for 6 weeks	No	Good
Calachanis et al., 2004/case report [26]	72 years	PFO	Cardiostar PFO-0335M	Amoxicillin	4 weeks	TEE: 2 vegetations, 8, and 13 mm LA side of device	*Candida albicans*	Vancomycin+gentamicin+difluconazole, later imipenem and levofloxacin for 6 weeks	No	Good
Goldstein et al., 2002/case report [54]	42 years	PFO	CardioSEAL device, 23 mm diameter	Not given	10 weeks	TTE/TEE: 1,7 mm vegetation LA side of device	*Bacillus punilis*	Vancomycin later during follow-up	Yes	Good
Bullock et al., 1999/case report [25]	10 months	ASD II	Amplatzer septal occluder	n.d.	7 weeks	TEE: vegetation RA	*Multiresistant Staphylococcus aureus*	Vancomycin, gentamicin	Yes	Good
Balasundaram et al., 2005/ case report [14]	8 years	ASD II	Amplatzer septal occluder	n.d.	3 months	TTE: no vegetation TEE: vegetation LA	*Klebsiella pneumoniae*, *Acinetobacter* spp.	Linezolid, cefotaxime for 4 weeks; relapse treated with cefoperazone–sulbactam, vancomycin, rifampicin	Yes[a]	Good
Sievert et al., 1998/clinical study [117]	2 of 200 patients: 54 years	ASD II	ASDOS	n.d.	6 months	n.d.	*Staphylococcus*, coagulase-negative	n.d.	Yes	Died (sternal wound infection)
	53 years	PFO	ASDOS	n.d.	2 weeks	n.d.	*Staphylococcus aureus*	n.d.	Yes	Died (after operation)
Wilkinson et al., 1998/clinical study [133]	1 of 26 patients: age n.d.	ASD II	Amplatzer septal occluder	n.d.	6 weeks	TEE: vegetation	*Staphylococcus aureus*	n.d.	Yes	Good
Dyck et al., 1988/clinical study [44]	1 of 40 patients: age n.d.	PDA	Rashkind umbrella occluder	Not given	9 days	n.d.	*Staphylococcus aureus*	Intravenous antibiotics for 6 weeks	No	Good
Powell et al., 1995/clinical study [104]	1 of 44 patients: age n.d.	Obstructed RV-PA conduit	Palmaz stent	Cefazolin	5 weeks	n.d.	n.d.	Intravenous antibiotics for 4 weeks	No	Good
Li et al., 1998/ clinical study [83]	1 of 185 patients: age n.d.	LPA stenosis	LPA stent	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

ASD II secundum type atrial septal defect, *ASDOS* atrial septal defect occlusion system, *LA* left atrium, *LPA* left pulmonary artery, *LV* left ventricle, *MV* mitral valve, *n.d.* no data, *PDA* patent ductus arteriosus, *PFO* patent foramen ovale, *RV-PA conduit* right ventricle-to-pulmonary artery conduit, *TEE* transesophageal echocardiography, *TTE* transthoracic echocardiography, *TV* tricuspid valve, *VSD* ventricular septal defect

[a] During surgery, small vegetations were found on the left and right sides of the device

1.3% for tetralogy of Fallot; 2.7% for VSD; 2.8% for primum type ASD; 3.5% for coarctation of aortic arch; and 13% for aortic valve stenosis. A 20-year follow-up in transposition of great arteries revealed a cumulative incidence of IE of 4.0% and a 10-year follow-up in complete ASD of 1.1% and in pulmonary atresia with intact ventricular septum of 5.3% and with VSD of 6.4% [96]. Importantly, for risk assessment, emphasis has to be put on prosthetic material and its impact on cardiovascular device-related infections (Table 3) [8, 33, 34, 38, 53, 58, 65, 69, 72, 79, 83, 84, 88, 97, 108, 119, 137].

Palliated CHD

Patients with complex CHD with functionally univentricular malformations have become treatable by cardiac surgery with the Norwood and Fontan procedures (Fig. 1) [16, 34, 38, 65, 72, 83, 88, 97, 137]. Patients after univentricular palliation of complex CHD with functional univentricular malformations leading to bidirectional Glenn anastomosis and Fontan procedure survive until adulthood but remain at lifetime risk for IE due to frequent use of prosthetic material [34, 38, 65, 72, 83, 88, 97, 137]. Patients palliated by an aortopulmonary shunt remain at lifetime risk as well [24, 134]. These patients can be predicted to increasingly contribute to future numbers of post-interventional IE, which currently account for >15% (Fig. 3) [34, 38, 65, 72, 83, 88, 97, 137].

Prosthetic material

Increased IE risk following cardiac surgery [96] and catheter-related cardiac interventions is mainly linked to implantation of prosthetic material or cardiovascular devices, independent of underlying CHD [82, 83, 97, 118, 119]. The types of prosthetic material implanted with permanent bloodstream contact are increasing (Table 3). Prosthetic material is biological (animal or human heart valves, sterilized by 1% glutaraldehyde and 20% isopropyl alcohol) or non-biological (metal alloys or synthetic material used for cardiovascular devices, such as stainless steel, platinum, polytetrafluorethylene, pyrolytic carbon, polyvinyl chloride, silicone, polydioxane, or polyglactic acid). Pacemaker systems with intracardiac electrodes account for most cases of intracardiac device-related IE [71]. Interventional closure of ASD or VSD, stent implantation, or closure of patent ductus arteriosus may also be followed by IE (Table 2) [14, 25, 26, 44, 54, 97, 104, 109, 117, 133]. Effects of various foreign materials may differ considerably but have not been properly studied in patients with CHD.

Sources of bacteremia

The risk of IE may be associated with various sources of bacteremia. In adolescents with CHD, lifestyle habits such as piercing, tattooing, nail biting, but also animal bites, skin disorders such as acne, or intravenous drug abuse are potential sources of bacteremia [7, 113]. IE by itself predisposes in 2.7% for a second IE episode at the same location [9]. Medical procedures, including dental care [8, 33, 34, 38, 42, 65, 68, 69, 72, 74, 83, 84, 88, 97, 99, 108, 116, 119, 122], cardiac surgery [8, 38, 65, 67–69, 72, 74, 83, 88, 97, 99, 108, 116, 119, 137], catheter-related procedures [68, 69, 72, 83, 88, 97, 116, 119, 137], and other non-cardiac invasive procedures [33, 38, 42, 65, 67–69, 72, 74, 83, 84, 122, 137] are potential causes for bacteremia in up to 46%, 18%, 20%, and 20% in cases of CHD-associated IE, respectively. Until recently, antimicrobial prophylaxis was recommended for these procedures [134]. Amoxicillin prophylaxis reduces bacteremia in children after dental procedures from 84% to 33% [85]. Prophylaxis, however, may fail due to patient-related factors (compliance) in up to 40%, physician-related factors (knowledge) in 50%, and ineffective drugs against rare pathogens in 66% [33, 38, 42, 65, 68, 69, 72, 73, 83, 84, 88, 97, 108, 116, 119, 122, 137]. Nowadays, bacteremia from daily care activities is judged a far greater risk [134].

Other risk factors

Previous IE remains a substantial risk factor predisposing to recurrent IE [134]. Age may be another risk factor as IE peaks in infancy and late adolescence [36]. IE in preterms, neonates, or infants younger than 2 years of age is related to other risk factors than in older patients with CHD [35, 91, 101]. Leading risk factors are prematurity with immune compromise and central venous access with catheter-related blood stream infections [94]. Normal cardiac structures may be affected, and the incidence of fungal IE is up to 10% [15, 36, 80, 93].

Recently, the life-long risk of infective endocarditis has been determined for ACHD patients at an age of 18 years during transition by complex statistical data analysis in a nationwide Dutch registry. Risk factors such as gender, type of CHD, and complications of CHD during childhood (<18 years) were used to predict risk of IE at the end of the fourth and sixth decade of life and to discriminate in a high (≥3%) and low (<3%) risk patient population groups [128].

Microbiology

Most cases of CHD-associated IE are caused by *Streptococcus* spp. (44%; 95% confidence interval (CI), 39.4–48.6, as calculated from literature), including *Streptococcus viridans* group (*Streptococcus mutans*, *Streptococcus sanguis*, *Streptococcus mitis*) and *Enterococcus* spp. [8, 9, 21, 33, 38, 42, 47, 53, 58, 65, 67–69, 73, 74, 83, 84, 88, 97, 99,

Table 3 Catheter-based devices and surgery-based foreign material for the treatment of congenital heart disease

Treatment modality	Device type	Reasons for use of devices or foreign material	Material involved
Catheter-based	Closure devices	Atrial septal defect Patent foramen ovale Patent ductus arteriosus Ventricular septal defect Paravalvular leaks[b] Collateral blood vessels[c]	Nitinol, 316L stainless steel, platinum, teflon, polyurethane, homologous pericardium, ivalon, polyester fabric, polytetrafluorethylene, latex, nylon, phynox, chromicum, nickel, titanium, molybdenum, cobalt
	Stents[a]	Branch pulmonary artery stenosis Coarctation of the aorta Patent ductus arteriosus Patent foramen ovale Systemic/pulmonary vein stenosis Peripheral vascular disease/carotid artery transcatheter valve repair	316L stainless steel, platinum, iridium, nickel, titanium, molybdenum, cobalt, tantalum, polytetrafluorethylene, bovine jugular vein
	Miscellaneous	Electrophysiological cardiac devices[d] Ventricular assist devices[e] Venous or arterial line Vena caval filters Ventriculoatrial shunts Vascular closure devices Peritoneal dialysis Hemodialysis, filtration Pledgets	Polyvinyl chloride, stainless steel, titanium, nitinol
Surgery-based	Closure device	Patches	Homologous pericardium, polytetrafluorethylene, polyester fabric
	Sutures	Artificial or biological	Polydioxanone, polyglactic acid, polyglycolic acid, polypropylene
	Heart valves	Mechanical	
		Biological (homograft, xenograft)	Bovine jugular vein[f]
	Vascular conduit	Shunt	Polytetrafluorethylene
	Vascular grafts	Biological vessel (veins and arteries) Hemodialysis	
	Clips	Extracardial/vascular	Stainless steel
	Tubes	Drainage	Polyvinyl chloride, silicone

[a] Including different type of stents such as bare metal, covered, drug eluting, biodegradable, stented valves, stent grafts

[b] Including perforated sinus of Valsalvae

[c] Including aortopulmonary collateral vessels in pulmonary atresia/tetralogy of Fallot; systemic artery to pulmonary collaterals and venovenous collaterals after bidirectional Glenn and Fontan procedures; systemic arteriovenous fistulae such as vein of Galen malformation, hepatic arteriovenous malformation, hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome); pulmonary arteriovenous fistulae; coronary artery fistulae; aortopulmonary surgical shunts

[d] Including pacemaker, implantable cardioverter defibrillator, biventricular pacing/cardiac resynchronization therapy, pacing leads, pacemaker generator

[e] Including extracorporeal membrane oxygenation, left ventricular assist devices, total artificial hearts, intra-aortic balloon counterpulsation catheters

[f] Sterilized in 1% glutaraldehyde and 20% isopropyl alcohol

108, 110, 116, 119, 122, 127, 137] and by *Staphylococcus* spp. (27%; 95% CI, 23.4–30.8; *Staphylococcus aureus*, coagulase-negative staphylococci), the most frequently (>50%) isolated organism in cardiovascular device-related infections [11, 65]. Gram-negative HACEK group bacteria, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*, or miscellaneous microorganisms and fungi cause 16% (95% CI, 11.9–19.3) of cases. Culture-negative IE is found in 12% (95% CI, 8.5–15.9). Gram-negative

bacteria are more frequent in IE associated with CHD compared to adults with IE not associated with CHD [102, 121]. Therefore, the pathogen array in CHD contrasts that in adult IE without CHD, where *Staphylococcus* spp. (40%) dominates, followed by oral streptococci (31%), non-oral streptococci (10%), and enterococci, or fungi (less than 10% each; Table 1) [24].

Clinical manifestations and episode-related complications

Clinical course

Clinical signs and symptoms of IE associated with CHD are variable, insidious, and usually unspecific [28]. Two clinical courses are distinguished: *acute IE*, a severe life-threatening disease often characterized by fulminant onset, high rate of complications leading to congestive heart failure (CHF), and high rate of surgical intervention required for treatment, and *subacute IE* which shows a subtle course, often blurred by antibiotics [24, 77]. Subacute IE in children is associated with cardiovascular device-related infections after catheter interventional closure of ASD or VSD (Table 2) [8, 117]. The calculated mean interval between assumed start of bacteremia and first symptoms of IE in CHD is approximately 2 weeks [72], similar to the adult IE not associated with CHD caused by streptococci [120]. Only 16% of IE in CHD are diagnosed during this "incubation period." In the other cases, diagnosis is delayed by 7–12 weeks [68, 72, 81].

Clinical signs and symptoms

The most frequent signs and symptoms of IE in CHD are fever (>80%), often of low grade, malaise, fatigue, weight loss or failure to thrive, splenomegaly, myalgia, arthralgia, headache, chills, nausea, and vomiting [1, 8, 9, 20, 21, 33, 34, 38, 42, 47, 58, 65, 67, 68, 72, 74, 79, 83, 84, 88, 97, 99, 100, 107, 108, 110, 111, 116, 119, 122, 127, 137]. Specific clinical findings are less frequent (<20%). They include changing heart murmur or skin manifestations including Osler nodes, Janeway lesions, or Splinter hemorrhages, which are typical for IE, but can be observed in other diseases such as lupus or typhoid fever. Fever while on antibiotic therapy persists around 4.3 days, and blood cultures become negative after 0.7 days [88].

Cardiac episode-related complications

Potential episode-related complications of IE in CHD may localize inside or outside the heart [8, 9, 20, 21, 33, 34, 38, 42, 47, 53, 58, 65, 67–69, 72, 74, 79, 83, 84, 88, 97, 99, 107, 108, 110, 111, 119, 127, 137]. CHF occurs in up to about half of the cases (range, 28–46%, as calculated from literature) and is the leading cause of hemodynamic compromise due to destruction of affected valves (22–32%) [8, 9, 20, 21, 33, 34, 38, 42, 47, 53, 58, 65, 67–69, 72, 74, 79, 83, 84, 88, 97, 99, 107, 108, 110, 111, 119, 124, 127, 137]. Rarely, CHF in IE may result from emboli to coronary arteries (<1%), myocarditis, arrhythmias (6–11%), perivalvular abscess (PVA), myocardial abscess formation, and intracardiac fistulae (0–7%) [3, 4, 8, 9, 20, 21, 33, 34, 38, 42, 47, 53, 58, 65, 67–69, 72, 74, 79, 83, 84, 88, 97, 99, 103, 107, 108, 110, 111, 119, 127, 137]. Involvement of atrioventricular node may cause atrioventricular block in up to 4% [8]. The frequency of episode-related complications is comparable to adults with structural heart disease despite their by far more frequent PVA [24, 40, 92]. As mortality after surgery in acute IE is increased, indication and timing of surgery are difficult to determine [105]. When myocardial function is reduced, surgery should be done before further hemodynamic deterioration occurs [96].

Extracardiac episode-related complications

Extracardiac episode-related complications of IE in CHD patients are frequent (up to 43%) and either caused by embolic events or immune phenomena [8, 9, 20, 21, 33, 34, 38, 42, 47, 53, 58, 65, 67–69, 72, 74, 79, 83, 84, 88, 97, 99, 107, 108, 110, 111, 119, 127, 137]. Infected heart valves and contaminated cardiovascular devices such as electrodes from pacemakers are sources of thromboemboli. No studies compare risk for embolism in patients with and without intracardiac devices. Episode-related complications are more frequent in vegetations >10 mm in size and in left-sided compared to right-sided vegetations [97], but not in multiple vegetations [9, 79]. Embolic episodes frequently lead to renal (10%), splenic (4%), pulmonary (28%), cerebral (16%), bowel (4%), or peripheral vascular/cutaneous (26%) infarcts. Neurological episode-related complications (33%) including stroke (16%), seizures (11%), abscess formation (5%), and hemiparesis (2%) may either constitute initial manifestation of IE or manifest years after its treatment.

Clinical signs and episode-related complications of cardiovascular device-related infections are similar to those of IE despite specific local and systemic clinical features [11]. In percutaneously introduced devices, clinical signs include local pain, induration, erythema, and purulent drainage and in subcutaneously implanted devices include cellulitis or abscess formation. Following pseudoaneurysm formation involving the vascular graft, a pulsatile mass can be detected on cardiac magnetic resonance imaging at site of anastomosis. Following vegetation and thrombus formation on intra- or extracardiac devices, clinical complications are embolisms to distal vessels either with direct vessel

occlusion or indirect immune-mediated ischemia. In addition, signs of bacteremia may manifest [11].

Diagnosis

IE should be suspected in CHD patients with persisting fever and newly manifesting CHF. Notably, IE in CHD after cardiac surgery occurs after a mean interval of 5.2 to 8.8 years [72, 74]. A prompt diagnostic workup includes repeated aerobe and anaerobe blood cultures, echocardiography, and inflammation parameter determination, the results of which are required for diagnosis of IE based on the modified Duke criteria [82]. Modified Duke criteria were shown useful also for diagnosis of IE in children [108].

Blood cultures

Positive bacterial blood cultures are one of the key indicators for diagnosis of IE. Their sensitivity in CHD-associated IE is 82% [1, 8, 9, 20, 21, 33, 34, 38, 42, 47, 58, 65, 67, 68, 72, 74, 79, 83, 84, 88, 97, 99, 100, 107, 108, 110, 111, 116, 119, 122, 127, 137]. In patients treated with antibiotics before blood collection, special blood culture techniques including automated systems using resin to bind antibiotics, thus facilitating bacterial growth despite antibiotics, should be used to avoid bias. Three sets of aerobe and anaerobe cultures should be drawn. Reasonable blood volumes are 1–3 ml for infants, 3–5 ml for toddlers and preschool-aged children, and 10 ml for school-aged children and adolescents [31]. Persistently positive blood cultures, defined as recovery of a microorganism consistent with IE, are two blood culture sets drawn more than 12 h apart, all three sets, or a majority of four or more separate blood culture sets, with first and last drawn at least 1 h apart [82]. To detect “hard to grow” microorganisms (HACEK group organisms or fungi) incubation should last 2–4 weeks [23].

Echocardiography

The second key diagnostic indicator of IE is echocardiography. Its sensitivity in CHD-associated IE is 60–80%, but lower in complex types of CHD and in postoperative course [8, 9, 20, 33, 34, 38, 53, 58, 79, 83, 84, 97, 107, 108, 127]. Diagnostic advantages of transesophageal echocardiography such as more precise visualization of vegetations have been validated for children [64]. Vegetations can be visualized by two-dimensional echocardiography (transthoracic as small as 2–3 mm and transesophageal 1–1.5 mm) [136]. The mean vegetation size is approximately 11.5 mm [97]. Valvular regurgitation can be seen with color Doppler echocardiography, and hemodynamic valvular compromise with pulsed or continuous wave Doppler echocardiography [55, 89, 90]. Moreover, echocardiography may visualize myocardial abscess formation, paravalvular abscesses, intracardiac fistulae, dehiscence of a prosthetic valve, pericardial effusion, or severe myocardial dysfunction. Guidelines for echocardiographic diagnosis of IE have been published for adults [29, 56, 136] but not for children with CHD, so far.

Intraoperative sampling

If surgery is required to replace infected valves or contaminated prosthetic material, samples for microbiological workup should be collected including cultures and molecular diagnostics such as eubacterial (as a screening tool) and pathogen-specific polymerase chain reaction assays [49].

Therapy

Antimicrobial therapy

In the mid-1940s, the introduction of penicillin changed IE from an almost certainly fatal to a curable condition (Fig. 1) [21, 30]. Treatment has become a multidisciplinary endeavor involving specialists for cardiology, cardiac surgery, infectious diseases, hematology, and other disciplines. Antimicrobial strategies must take two factors into account: (1) Infecting organisms exist in a state of reduced metabolic activity and are extremely densely packed inside vegetations and (2) cure of IE requires sterilizing vegetations.

Bactericidal rather than bacteriostatic agents must be used in high dosages and for sufficient time [131]. Combination of a beta-lactam and an aminoglycoside results in synergistic bactericidal effect [87]. Exceptions of this synergistic bactericidal approach are modern bacteriostatic antibiotics (linezolid or quinupristin/dalfopristin) [10].

Therapy should last >2 weeks, but causative microorganism, involved valve, and antimicrobial compound used must be taken into consideration. Antibiotics for 6 weeks or even longer may be required in cardiovascular device-related IE, which cannot be treated by surgery such as explantation of foreign material due to comorbidity [62]. To achieve higher serum drug levels, intravenous is preferable to oral therapy.

Adequate antibiotic dosing is related to the minimal inhibitory/bactericidal concentration of the compound against isolated pathogens. Optimal dosing frequency, interval, and administration procedure (bolus injection is superior to continuous infusion) depend on microorganism and antimicrobial agent used [17, 50]. Finally, timing of therapy initiation is important. The danger of delaying therapy

must be weighed against diagnostic importance of isolating microorganisms in blood cultures. Guidelines for antibiotic treatment of CHD-associated IE have been published by the AHA [13, 46], European Society of Cardiology (ESC) [57], and British Society for Antimicrobial Chemotherapy [45].

Cardiovascular device-related infections

Specific recommendations for cardiovascular device-related infections have been published in the past [11] and recently updated for cardiovascular implantable electronic device infections by the AHA [11, 12] and by the ESC [57]. Thus, since staphylococci are the most frequent pathogen, treatment best follows recommendations for healthcare associated IE or *S. aureus* IE (Table 2) [46]. Given the possibility of methicillin resistance, an initial empiric broad-spectrum therapy should include vancomycin until susceptibility testing of isolated microorganisms is available. Linezolid or quinupristin/dalfopristin may be used in patients with vancomycin intolerance/allergy or vancomycin-resistant enterococci [6]. The combination of antibiotic treatment with complete removal of contaminated device, if ever possible, is preferred [11]. The device removal has been proposed for closure devices of patent ductus arteriosus, ASD, and VSD [11]. Similar recommendations are given for peripheral arterial stent infections, apart from critical ill children where surgical removal is associated with high risk and therefore long-term antibiotic treatment is needed. [11]

Duration of antibiotic treatment in uncomplicated cases is >14 days after device removal and first negative blood culture, or 4 weeks in complicated cases with vegetations on the device, and 6 weeks for cardiovascular device-related infections in left ventricular assist devices comparable to prosthetic cardiac valve infections [11]. A long-term suppressive, even life-long antimicrobial therapy may become necessary [106].

Fungal endocarditis

Fungal endocarditis remains difficult to treat, and mortality approaches 50% [123]. Combined medical and surgical therapy is recommended [13, 93]. After intravenous antifungal therapy, it is often necessary to prevent an IE relapse; this should involve an ongoing long-term antifungal therapy, usually with an oral azole agent such as ketoconazole [106], fluconazole, or voriconazole, depending on susceptibility of fungi.

Microbiological monitoring during follow-up

Bacteremia may resolve within several days after initiation of effective antimicrobials, and 75% of patients become afebrile during first and 95% during second week of adequate antibiotic therapy [24]. Fever persisting beyond this period should trigger a repeated diagnostic workup, although drug fever as a side effect of antibiotics has to be considered. Blood cultures should be taken during, at the end, and 4 weeks after completion of antibiotic treatment to rule out recurrent IE [24].

Surgical management

Rates of surgery in pediatric patients with CHD-associated IE, either during or after IE, are 16% to 67% [39, 72, 98]. Recommendations for time-optimized cardiovascular surgery remain to be defined for patients with CHD-associated IE [46]. Pre- and postoperative complications, mortality, and length of hospital stay can be reduced, if surgery is performed early during IE and uses reconstructive techniques without foreign material [1, 61]. Risk-factor stratification for death due to CHD-associated IE has not been validated [59, 110, 111]. Nevertheless, surgery is considered for ACHD patients with ongoing sepsis despite antimicrobial treatment, large mobile vegetations on echocardiography with or without embolization, involvement of mechanical valve prosthesis, myocardial abscess formation suspicious for atrioventricular block, mycotic aneurysms, and fungal endocarditis [48, 135]. This strategy is comparable to that with IE not associated with CHD [105].

Development of IE after cardiac surgery such as shunt or conduit procedure is a potentially life-threatening complication. Antimicrobial treatment alone is often insufficient because prostheses are usually polytetrafluoroethylene tubes which require a surgical re-intervention with explantation of contaminated foreign material [96].

Prevention

The 2007 AHA revised guidelines for prevention of IE, the ACC/AHA 2008 guidelines for management of adults with CHD, and the 2009 guidelines of the ESC are focus on underlying cardiac conditions associated with the highest risk of adverse outcome and no longer on an increased lifetime risk for IE [57, 130, 134]. Nevertheless, the AHA stated difficulties determining contribution of a specific CHD type as independent IE risk factor because the number of published series of CHD-associated IE is limited. The AHA guidelines recognize changes of management strategies and their impact on the natural history of CHD. Indeed, CHD is operated earlier during infancy and, therefore, future numbers of patients with unrepaired CHD will further decrease. Complete repair of certain CHD types, such as VSD, eliminates the IE risk. Thus, the specific focus of the AHA guidelines is conceivable: unrepaired cyanotic CHD which is burdened with the highest risk for

adverse outcome, including palliative shunts or conduits, and repaired CHD with prosthetic material for at least 6 months following implantation, the period of incomplete endothelialization with residual defects [134]. Nevertheless, prospective studies have to carefully monitor the incidence of IE, especially for unrepaired VSD, bicuspid aortic valve stenosis, or patent ductus arteriosus, conditions for which antibiotic prophylaxis is no longer recommended [18].

Outcomes

Overall mortality of CHD-associated IE has decreased to 10% in 1990 (Fig. 1) [34, 65, 72, 79, 84, 97, 107]. Progress in diagnosing IE, improvements of antimicrobial treatment, cardiac surgery, and catheter interventional therapy contributed to the decrease (Fig. 1). For comparison, mortality of IE in adults with structural heart disease especially those aged >60 years is up to 30% (Table 1) [59, 86]. Mortality of surgery for IE remains high with 40% to 50% [34, 72, 97].

Sievert et al. reported a mortality of 1% due to staphylococcal infection after interventional closure of ASD [117], contrasting all other case studies or small clinical series with no deaths related to IE (Table 2). Factors predicting a worse outcome for IE in children CHD are delay of hospital admission, age <3 years, and a vegetation size >10 mm detected by echocardiography [2, 58, 79].

Conclusions

The risk for IE is distinct whether CHD is unrepaired, repaired, or palliated. Management of CHD has changed in the last 20 years. Most CHD have become treatable, and CHD patients may survive until adulthood. Patients with unrepaired CHD numerically decrease due to augmented cardiac surgery or catheter interventional therapy early in life. Concomitantly, patients with repaired CHD or palliated CHD numerically increase. ACHD patients form a novel patient group with distinct risk levels for IE throughout life. Complete CHD repair may eliminate the risk for IE, as exemplified in VSD. Residual defects after incomplete CHD repair and palliated CHD retain an IE risk. The new AHA and ESC guidelines focus on these patients.

In industrialized countries, IE in CHD is by far more frequent than in RHD. IE in CHD may evolve after implanting cardiovascular devices, and cardiovascular device-related infections emerge as a new type of infection. Streptococci are more frequently the cause than staphylococci except in cardiovascular device-related infections, and IE localizes more often in the left than in the right heart. Around half of the patients with CHD-associated IE develop severe episode-related complications. Nevertheless, the overall outcome of CHD-associated IE is better than of IE not associated with CHD, possibly due to fewer prosthetic valve endocarditis, *S. aureus* IE, co-morbidity, or complications leading to (secondary) surgery.

Future directions

Prospective investigation of differences between children and adults with CHD-associated IE is needed. For the growing population of adults with CHD surviving until middle age or longer, differences between IE associated with versus without CHD may be more pronounced. As adults with CHD may differ from adults with structural heart disease regarding epidemiology, risk factors, clinical presentation, complication rates, diagnosis, and outcome, this will have to be carefully studied. Finally, the impact of the new AHA and ESC IE prevention guidelines on IE epidemiology in children and adults with CHD needs to be monitored.

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