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The Role of Modern-Era Echocardiography in Identification of Cardiac Risk Factors for Infective Endocarditis

John F. Sedgwick and Gregory M. Scalia

Abstract

This chapter provides an updated overview of the scientific literature on cardiac pathology predisposing to infective endocarditis and the estimated risk associated with selected lesion-specific abnormalities, in an era of changing epidemiology and advanced echocardiographic imaging. Importantly, with the evolution of modern-era echo, subtle changes in valve structure and function are now easily detectable and a proportion of cases of apparently ‘normal’ valves involved with IE, may in fact have subtle pre-existing pathological and/or haemodynamic abnormalities. The chapter will have a clinical focus with an aim to provide the Physician with up-to-date and practical information on cardiac risk factor identification for infective endocarditis.

Keywords: echocardiography, infective endocarditis, risk factors, valvular heart disease, congenital heart disease, degenerative valve disease, rheumatic heart disease, cardiac pathology, disease incidence, modern-era

1. Introduction

Infective endocarditis (IE) risk is strongly associated with underlying cardiac disease. This chapter will review the pathology, mechanisms and estimated risks according to lesion-specific groups. Echocardiographic predictors of IE will be discussed along with the increasingly reported occurrence of IE in ‘normal valves’.
2. Predisposing cardiac disease: a changing epidemiology

Since mid-last century, the epidemiology of IE has continued to change across high-income countries (HIC), from predominantly young patients with rheumatic heart disease (RHD) to the current era of an ageing population with IE, infrequent RHD and prevalent degenerative valve disease (DVD). A history of acute rheumatic fever (ARF) in patients with IE had declined from ~38 to 22.5% in the 30 years up to 1967 [1]. By the 1980s, this had reduced to 6% [2]. According to data from the International Collaboration on Endocarditis—Prospective Cohort Study (ICE-PICS), DVD is the most common underlying pathology in IE, with significant mitral regurgitation (MR) and aortic regurgitation (AR) accounting for 43.3 and 26.3% of cases, respectively, compared with rheumatic mitral valve, present in only 3.3% cases. Prosthetic valve endocarditis (PVE) accounts for up to 22.2% of cases [3], whilst the prevalence of cardiac device-related infective endocarditis (CDRIE) has increased along with health-care associated IE (HCAIE) [4]. Endocarditis patterns in congenital heart disease (CHD) have changed due to patients surviving into adulthood with more complex disease, the availability of improved surgical techniques and implantation of prosthetic material [5, 6].

The 2015 European Society of Cardiology IE management guidelines now consider the following cardiac conditions to pose the highest risk of IE: (i) prosthetic cardiac valves and/or repairs with prosthetic material, (ii) previous IE, (iii) cyanotic CHD, and (iv) any CHD that has been repaired for up to 6 months post procedure or indefinitely if a residual defect or valve incompetence persists. Repair or intervention includes both surgical and transcatheter procedures. Antibiotic prophylaxis is recommended for these patients when exposed to procedures considered high-risk [7].

3. Estimating risk of infective endocarditis: methodological issues

There are methodological challenges with investigating risk of acquiring IE. Two major limitations are: i) low incidence of IE in the general population and ii) selection bias associated with tertiary referral hospitals. Variations in study design and methodology also contribute to the difficulties faced in drawing generalised conclusions.

4. Pathogenesis of infective endocarditis with underlying cardiac disease

The major predisposing categories of underlying cardiac pathology are DVD, CHD and RHD. Platelet-fibrin aggregates form on damaged or inflamed endothelium, resulting in nonbacterial thrombotic endocarditis (NBTE), a precursor of IE [8]. Microorganisms are able to attach to this nidus via adhesion molecules and stimulate a host inflammatory response [8].
Regurgitant valves are at higher risk of IE than stenotic valves [9]. In a large clinical-pathological study on native valve endocarditis (NVIE), 84% of valves were regurgitant [10]. Another study found the majority of cases of IE presenting to surgery were for regurgitant valves compared to a control-group of non-IE cases undergoing surgery (9% of regurgitant bicuspid aortic valves (BAV), 1.2% of calcified BAVs, 1.6% of calcified trileaflet aortic valves (AV) and 7% of mitral valve prolapse (MVP)) [11]. Aortic regurgitation (AR) is a predisposing lesion in 17–36% of cases of IE, whilst mitral regurgitation (MR) accounts for 10–18% [12].

The pathogenesis of IE in structural cardiac abnormalities is characterised by the hydrodynamic theory [13]. A high velocity turbulent jet exerts a shearing effect on endothelium, at the site of a restrictive orifice (e.g. ventricular septal defect (VSD) or MR jet) and/or a distal point of contact (jet lesion). The narrowest diameter of flow is the vena contracta (VC), just distal to the restricted anatomical orifice. This is where the pressure is minimal and retrograde flow may occur, permitting platelets and bacteria to deposit [13]. The typical location of vegetation is on the upstream side of the valve, that is, the atrial aspect of the MV, tricuspid valve (TV) and ventricular aspect AV, pulmonary valve (PV) [9].

Structurally normal native right-sided valves in the absence of significant pulmonary hypertension, are exposed to lower pressure flows and are far less commonly involved with IE. In children, without CHD, native right-sided IE involving normal valves is rare but may occur in association with trauma to the valve from central lines or catheters [14, 15]. Other factors are important in risk of acquiring IE and include an interplay between microorganism virulence, altered host defence mechanisms, predisposing systemic illness, and environmental and social factors [16].

5. Structurally normal native cardiac valves

Infective endocarditis does occur in some patients without pre-existing known structural abnormalities. Whether the valves were completely normal is uncertain. Early degenerative changes can be present without clinical detection [17]. Modern-era echo with high image resolution and careful scrutiny of valve morphology and function, has the potential to shed more light on this research question.

There is an increasing prevalence of IE involving structurally normal cardiac valves, accounting for 26–43% of native left-sided IE cases [2, 18, 19]. Sun et al. [18] reported the commonest underlying cardiac predisposition was mitral valve prolapse (MVP) followed by normal valves (26%). Olmas et al. [20] found in an IE cohort, normal left-sided native valves in 39.8% of patients aged >65 years and in 53.8% of those aged ≤65 years, whilst DVD comprised 23.4% of the cohort. However, details regarding Doppler valve function were not available. This is important, for even normal valves may be regurgitant, exposing endothelium to shearing forces. Limitations include assessing valves for pre-existing pathology when already involved by infection and absence of pathological correlation to exclude subtle underlying pathology. In vitro studies have demonstrated certain microorganisms can attach to and/or be internalised by healthy valve endothelium, however in vivo, animal studies have required trauma to the endothelium to initiate IE following an inoculum of bacteria [9]. This raises the
question—are the valves ‘normal’ or are there subtle pathological changes or haemodynamic disturbance, which predispose to IE. This was also raised by Que and Moreillon [21] and Baddour et al. [9].

To assess normal valve thickness according to age, 200 normal valves were reviewed at autopsy [22]. There was approximately double the thickness of the aortic cusps and mitral leaflets with age [22]. In a separate study, transoesophageal echo (TOE) identified normal MV thickness overall to be ≤3 mm and AV≤2 mm in those aged <60 years [23]. The prevalence of normal valves with physiological regurgitation was investigated in a retrospective echocardiographic study of 1333 patients without a history of cardiac disease or hypertension [24]. Physiological MR and TR were defined as structurally normal valves on 2-D imaging, with a regurgitant jet area occupying <20% of the left atrial (LA) area and <5 cm² within the right atrium (RA), respectively. Aortic regurgitation with jet to LVOT width ratio <25% and normal leaflets was considered physiological. Non-organic MR was detected in over 4/5th of persons across all age cohort groups (10–89 years). Non-organic TR was identified in over 4/5th of persons across all age cohort groups (10–89 years). Non-organic AR was present in <10% of patients under 50 years, with an increase in prevalence corresponding to each decade, up to 46% of those aged 80–89 years [24].

5.1. Risk of endocarditis in normal valves with physiological regurgitation

Data is not readily available on the risk of IE in patients with left-sided non-organic regurgitation. However, one study did assess the risk of IE in structurally normal right-sided cardiac valves in adult patients with CHD and pulmonary hypertension (PHTN) [25]. Both TVs and PVs had physiological regurgitation. The presence of PHTN was responsible for increased regurgitant velocities across the valves and thought to mimic the haemodynamic forces experienced by incompetent left-sided valves. High velocity flow was defined as PR jet ≥3.2 m/s and TR≥4.7 m/s. A small subset of valves was inspected at necropsy with the majority of TVs and minority of PVs revealing mild nodular degenerative changes along leaflet closure margins. The echocardiograms were said to be normal in appearance. There were 0.61 and 7.17 cases of IE per 1000 patient-years in the normal valve group compared to the CHD control group, respectively. The risk was therefore small, but inconclusive due to insufficient patient numbers [25].

6. Degenerative valve disease

6.1. Degenerative disease of the aortic valve

The prevalence of nonrheumatic AS increases with ageing [26]. In a cohort of older patients with IE, the prevalence of acquired MR and AS was reported as 57 and 28% respectively, compared with 38 and 10% in patients <65 years [26, 27].

6.1.1. Fibro-calcific degeneration

Age-related findings often begin on the aortic valve in early or middle adulthood and include the following: (i) noduli arantii—fibroelastic proliferation on the ventricular surface of the
cusps, from early adulthood, most pronounced on the noncoronary cusp, (ii) ridge-like thickening at the base of cusps where mechanical forces are highest; occurs in early adulthood in 20–40% persons, and (iii) commissural adhesion, due to fibroelastic hyperplasia, affecting 10–20% of older persons [28]. With ageing, endothelial dysfunction and hemodynamic stress lead to degenerative changes, inciting an inflammatory process, not unlike atherosclerosis. Histological changes include subendothelial thickening, lipid and protein accumulation, inflammatory cell proliferation, fibrosis and calcification within the valve fibrosa [29]. The process is accelerated over the age of 55 years, and onset in males is marginally earlier than females [28]. Initially there is no significant restriction to cusp opening and the diagnosis of aortic sclerosis is confirmed with echo.

6.1.1.1. Aortic sclerosis and echocardiography

The presence of aortic sclerosis (focal thickening, no commissural fusion, peak velocity <2.0 m/s) is associated with an increased risk of death [30]. Caution should be exercised not to over diagnose sclerosis on echo [31]. Artefactual thickening and echogenicity can appear with harmonic imaging and over-gained signals. Optimising transthoracic (TTE) image settings and use of both harmonic and fundamental frequencies can overcome these limitations [31]. Transoesophageal imaging has higher resolution and anatomical detail is superior [31].

6.1.1.2. Aortic stenosis and risk of endocarditis

Eventually large calcified deposits occupy the body of the leaflet and can extend into the ventricular septum, the ventricular surface of the anterior mitral valve leaflet (AMVL) and are associated with mitral annular calcification (MAC). Cusp motion becomes restricted and aortic stenosis (AS) ensues. Ulcerations and thrombi may form, being a potential mimicker of IE [16, 32], and may form a nidus for infective endocarditis. There is a paucity of data on IE occurring with aortic sclerosis, although empirically, the risk is very small. Endocarditis of calcific trileaflet AS is relatively uncommon. According to Delahaye [33] 27/366 cases of native valve IE were pure AS. Risk is higher in patients with BAV and/or AR. In a study from the Mayo clinic [10], 310 native valves were excised for IE and it was reported 59% had no calcification. Mild-moderate and severe calcification was present in 37% and 5%, respectively. The most common underlying cardiac structural abnormalities were BAV (38% of 170 aortic valves) and MVP (43% of 120 mitral valves). This finding would suggest that IE is less common in severely calcified valves [10]. Another study with pathologic correlation found pre-existing calcification present in 27% of valves with IE, though numbers in the study were small [11].

Acquired degenerative changes of the AV leaflets can occur secondarily in the context of conditions leading to annuloaortic dilatation. In this pathology, the leaflets come together at the free edges rather than the zone of coaptation, leading to focal thickening, and increased risk of NBTE and IE [17].

6.1.1.3. Fenestrations

Acquired age-related fenestrations form within the lunular region of the aortic semilunar cusps, adjacent to the commissures, often in association with myxomatous AV disease.
Fenestrations are found in approximately 5% of females and 10–20% of males, mostly present from the age of <45 years with a minor increase in prevalence over time, in males [28]. They are not routinely identified on echo because of their location above the line of closure. Fenestrations result in valvular regurgitation in the following circumstances: (i) spontaneous rupture resulting in a flail cusp, (ii) fenestration enlarges to extend below the zone of coaptation and/or (iii) reduced leaflet coaptation, such as prolapse or root dilatation, when the fenestration is no longer ‘sealed-off’ within the cusp closure zone [34, 35]. The risk of IE associated with fenestrations or valvular perforations is unknown.

6.1.1.4. Lambl’s excrescences

Lambl’s excrescences increase in prevalence with age and may become incorporated into the noduli arantii [28]. They are located along the lines of cusp closure of left-sided (high pressure) valves. They are composed of a fibro-elastic core with an endothelial layer covering the surface. There is associated turbulence and relative stasis of blood flow, which predisposes to formation of NBTE and IE [34]. Although the risk of IE is unknown, empirically it is uncommon. Occasionally Lambl’s excrescences can mimic vegetation and lead to a false-positive diagnosis of IE. However, Lambl’s are usually identified as thin single or multiple filamentous strands on echo, which help differentiate them from typical vegetations and papillary fibroelastomas.

6.1.2. Myxomatous degeneration

Primary myxomatous degeneration (PMD) of the AV is less common than of the MV. In cases of significant ‘pure’ AS, it has been said to be the primary underlying pathology in up to 10–36% of subjects [38], however other pathological studies examining excised regurgitant aortic valves have reported much lower rates of PMD, at 2% [36] and in a more recent clinicopathological correlation study from China, 3% (35 of 1080 excised aortic valves) [37]. Histological findings include degeneration of the fibrosa layer, disruption of collagen fibres and deposition of mucopolysaccharides [37]. The cusps are susceptible to developing fenestrations adjacent to the commissures and with time, the prolapsing cusps develop thickening of the free margin, thought secondary to chronic trauma from the regurgitant jet [38]. The incidence of endocarditis with this pathology is unknown, however empirically, high velocity regurgitant jets increase the risk of IE.

6.2. Degenerative disease of the mitral valve

6.2.1. Mitral valve sclerosis and age-related changes

Mitral valve sclerosis is commonly encountered in the elderly and characterised by leaflet thickening. In patients >60 years, the leaflets are at least twice the thickness compared to early adulthood [22]. The following changes are frequently noted on the anterior leaflet: (i) senile sclerosis - nodular thickening on the atrial surface of the closing edge, up to age of 65 years, (ii) atheromatosis—age-related lipoid deposition (yellow plaque) on the ventricular aspect of the base of the leaflets extending towards and sometimes involving
the chordal apparatus [28]. The following changes may be noted at the posterior leaflet: (i) puckered scars—infrequent at 3–5%, >65 years, (ii) fibro-elastic hyperplasia (mitral opaqueness) of the atrial surface in ~20%, >65 years and, (iii) mucoid or myxomatous degeneration (~ 5–10%) ± prolapse, with increased proteoglycans in the spongiosa layer [28]. The condition shows a slight increase with age in the milder forms. Severe forms of mucoid change were not related to age [28]. Fibroelastic deficiency (FED) is seen more commonly in the elderly and can lead to leaflet prolapse and/or chordal rupture.

Mitral annular calcification (MAC) is common in the elderly though can occur prematurely in certain other conditions such as hypertrophic cardiomyopathy (HCM), PMD, diabetes and renal disease. MAC commonly involves the posterior annulus and parallels AV calcification, with a sharp rise >55 years [28]. Normal sphincteric action of the annulus is altered and MR ensues [17]. Inflammation accompanies MAC and complications such as ulcerative erosion, thrombus formation, systemic embolic, liquefaction necrosis, infected vegetations and abscess formation occur with increased frequency [34, 39]. With large protruding MAC deposits, it is theorised there is alteration of local blood flow, predisposing to NBTE and IE [39]. Mitral stenosis can also occur as calcium encroaches on the leaflets. Vegetations form at the base of the mitral leaflet [39] rather than the leaflet closure line, as seen with typical regurgitant lesions [17] and are localised accurately with 3-D echo. Although MAC predisposes to IE, the exact risk is unknown.

6.2.2. Myxomatous mitral valve disease and prolapse

Mitral valve prolapse (MVP) most commonly occurs due to PMD. Secondary myxomatous degeneration can occur in other conditions, such as RHD and age-related degeneration. Additional causes of prolapse include congenital and papillary muscle dysfunction. The ‘middle’ tissue layer of healthy valves, the spongiosa, normally thickenings towards the leaflet/cusp margins and this is not a pathological finding [16]. With pathological myxomatous changes, there is diffuse increase in deposition of glycosaminoglycans in leaflets, cusps, chords and annuli and thrombi may form [16]. In a study from China, echocardiography (either TTE or TOE) correctly identified valve prolapse and thickening in 85% of patients in which myxomatous disease was confirmed pathologically [37].

6.2.2.1. Prevalence of mitral prolapse and regurgitation in healthy individuals

In a landmark study, data was collected from a healthy population comprising the offspring of the original Framingham study group [40]. Echocardiographic criteria (2-D) used in the study were as follows: (i) prolapse - superior displacement of the mitral leaflet(s) >2 mm above the atrioventricular annular plane in the long-axis window, (ii) classic MVP - at least 2 mm prolapse with leaflet thickness ≥5 mm and, (iii) non-class MVP – ≥2 mm prolapse with leaflet thickness <5 mm [40]. A total of 2.4% met criteria for prolapse. Classic MVP was found in 1.3% of persons and non-classic MVP in 1.1% [40], with mean age mid 50s and a slight female preponderance. Mean MR volume was mild in the classic group and a trace in the non-classic and control groups. Severe MR was only found in the classic groups and comprised 7% of cases [40].

6.2.2.2. Prevalence and risk of mitral prolapse in endocarditis

Mitral valve prolapse occurs in 7–30% of cases of native valve IE, nearly always in the presence of MR and associated with redundant leaflets. Of note, NBTE forms on atrial aspect of thinned, redundant leaflets [17]. In a large clinicopathological correlation study of 120 native mitral valves excised due to IE, 43% had a history of prolapse [10]. The estimated risk of IE is shown in Table 1. Recent data published by Katan et al. [41] found a higher incidence of IE in MVP compared to earlier publications, thought in part due to the previous overestimation of true MVP in healthy individuals using less stringent diagnostic methods [41].

6.2.2.3. Mitral prolapse—echocardiographic predictors of endocarditis risk

Mitral regurgitation confirmed on echo and/or typical murmur, has been shown to be a predictor of risk in studies that have specifically assessed this variable (Table 1). In the study by Katan et al. [41], no cases of IE occurred in patients without a history of MR during follow-up. Nishimura et al. [47], found redundant leaflets (i.e. M-mode thickness ≥5 mm) were associated with IE, though numbers were small. Marks et al. [48] also confirmed classic MVP with leaflet thickening ≥5 mm (2-D echo) and redundancy was associated with IE risk over non classic MVP.

6.3. Degenerative disease of the right-sided cardiac valves

Gross degenerative changes of the right-sided valves are uncommon compared to the higher-pressure environment of left-sided valves. The TV often undergoes only minimal change, with nodular thickening along the closing edge of the anterior valve leaflet. Mild diffuse leaflet thickening may occur in middle age; though in a minority of patients (>65 years), may become moderate or severe [28]. Myxoid degeneration of TV leaflets occurs occasionally [49], with TV prolapse (TVP) and PMD occurring in about 4% of cases [37, 40] . The risk of IE in TVP is unknown. The pulmonary valve (PV) remains translucent and thin in the vast majority. Nodular thickening (noduli Morgani) along the centre part of the closing margin occurs in 50% of subjects,

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall incidence of IE in MVP (risk per 1000 patient-years)</th>
<th>MVP with regurgitation (risk per 1000 patient-years)</th>
<th>Overall incidence of IE in MVP with murmur (risk odds ratio – ‘OR’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katan et al. [41]</td>
<td>0.87</td>
<td>0.63; 2.9; 7.16</td>
<td></td>
</tr>
<tr>
<td>Clemens et al. [42] and Tay and Yip [43]</td>
<td>0.38</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Retchin et al. [44]</td>
<td>0.3</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Hickey et al. [45]</td>
<td>0.14</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Danchin et al. [46]</td>
<td>n/a</td>
<td>n/a</td>
<td>14.5</td>
</tr>
</tbody>
</table>

1Less than moderate MR.
2At least moderate MR.
3Flail leaflet.

Table 1. Risk of infective endocarditis associated with mitral valve prolapse and regurgitation.
increasing gradually with age [28]. The mild age-related degenerative changes of the PV are not typically associated with IE.

7. Congenital heart disease

7.1. Overall incidence of endocarditis in congenital heart disease

Recently published research estimates the incidence of adult congenital heart disease (ACHD)-associated IE is 1.0–1.33 cases per 1000 patient-years and in children (0–18 years), 0.41 cases per 1000 patient-years. Cumulative first incidence of IE, from birth to 18 years, was shown to be 6.1/1000 [5, 50, 51]. According to published data from the USA, the estimated incidence in children is lower, at 0.05–0.12 cases per 1000 patient-years [52, 53]. Interestingly, Marom et al. found 18% of children with IE had no underlying structural heart disease and no identifiable risk factors, compared to earlier published rates, ranging from 2.5–19% [54].

7.2. Incidence of endocarditis in complex congenital heart disease

Incidence rate in complex CHD has recently been published by Kuijpers et al. [5], 2017. Incidence of IE (per 1000 patient-years) reported according to lesion-specific pathology include: pulmonary atresia (PA) with ventricular septal defect (VSD), 7.84; double outlet right ventricle (DORV), 3.59; Marfans, 2.35; univentricular heart (UVH), 1.9; Tetralogy of Fallot (ToF), 1.8; congenitally corrected transposition (cTGA), 0.93; transposition, 0.89; and Ebstein’s anomaly, 0.7.

7.3. Endocarditis in simple shunts

7.3.1. Ventricular septal defect

Overall estimated incidence of IE with a VSD in ACHD is 1.0–1.33 and for children, 0.41 per 1000 patient-years (Table 2). In another study, the incidence was reported at 1.86 in adults and 1.06 in children, per 1000 patient-years (p = 0.06) [55]. The majority of studies have identified the following risk factors: i) unrepaired VSD ii) co-existent AR and, iii) residual defect at site of VSD repair. It has not been unequivocally proven a restrictive defect carries a higher risk. A VSD associated with AR carries a 2x relative risk (incidence increase from 1.25 up to 3.48/1000) [55], whilst a VSD that has undergone secondary aneurysmal transformation to form a Gerbode defect (LV-LA shunt) carries a risk of 5 per 1000 patient-years [56]. In one study, non-operated VSD’s carried a 2.6x risk (0.73 versus 1.87/1000 patient-years) [55].

7.3.2. Atrial septal defect

Secundum ASD IE incidence is estimated at 0.23 for children and 0.28–0.64/1000 patient-years in adults (Table 2). A higher than expected risk was likely due to concomitant valve disease or misdiagnosed primum defects [50]. Isolated ASD is rarely associated with infective endocarditis [57]. The risk in adults with atrioventricular septal defect (AVSD) is estimated at 0.89 per 1000 patient-years (Table 2).
<table>
<thead>
<tr>
<th>CHD</th>
<th>ASD; VSD; AVSD; PDA</th>
<th>Left-sided(^1)</th>
<th>Cyanotic (complex/conotruncal)(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuijpers et al. [5] (ACHD; Included prosthetic valves)</td>
<td>Incidence (per 1000 pt. years)</td>
<td>1.33</td>
<td>1.89; 0.57</td>
</tr>
<tr>
<td></td>
<td>Adjusted HR (95% CI)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mylotte et al. [51] (ACHD; Excluded prosthetic valves; Included conduits and repairs)</td>
<td>Incident IE (per 1000 pt. years)</td>
<td>1.0</td>
<td>1.61; n/a</td>
</tr>
<tr>
<td></td>
<td>Adjusted OR(^5) (95% CI)</td>
<td>n/a</td>
<td>5.11 (3.6–7.25); n/a</td>
</tr>
<tr>
<td>Rushani et al. [50], (Paediatric)</td>
<td>Incidence (per 1000 pt. years)</td>
<td>0.41</td>
<td>0.44; n/a</td>
</tr>
<tr>
<td></td>
<td>Adjusted Rate Ratio (95% CI)</td>
<td>n/a</td>
<td>1.88 (1.01–3.49); n/a</td>
</tr>
</tbody>
</table>

\(^1\) Left-sided includes: coarctation, aortic and mitral disease (Mylotte et al. and Rushani et al.); or LVOTO (left ventricular outflow tract obstruction), Marfan, BAV, CoA, MV defect, other LVOT (Kuijpers et al.).

\(^3\) Cyanotic (complex/conotruncal) includes: PA + VSD, DORV, UVH, ToF, TGA, Other (Kuijpers et al.).

\(^5\) Odds ratio when referenced to ASD, PDA, R-sided groups.

Table 2. Contemporary estimates of incidence and risk hazard ratios for infective endocarditis in children and adults with congenital heart disease, across selected lesion-specific groups.
7.3.3. Ductus arteriosus

The estimated risk of IE with patent ductus arteriosus (PDA) is 0.24 and 0.35 per 1000 patient-years in adults and children, respectively, whilst other data have shown for an unrepaired PDA, the IE risk is 0.35–1.4 per 1000 patient-years, in a mixed adult and paediatric cohort [12, 50]. According to one study, the risk of IE was only present <4 years of age, likely due to ligature procedure essentially eliminating IE occurrence in older children [50].

7.3.4. Echocardiography

Echo assessment of a VSD should include identification of vegetations or other IE complications, whether involving the defect, the valves or mural endocardium. Also, imaging must define shunt anatomy, efficacy of closure (where present), cardiac chamber size and function, pulmonary artery pressure and haemodynamics. Aneurysmal formation and Gerbode defect should be excluded. Echo is fundamental in the routine and peri-procedural assessment of ASD and other shunts. It is also important to note the presence or absence of an ASD (or other shunt) in valvular endocarditis. For example, an infected TV may be a source of paradoxical embolism. The direction of the regurgitant jet and shunt, along with the size and mobility of a vegetation are important factors when assessing the risk of embolisation.

7.4. Bicuspid aortic valve and aortic coarctation

Bicuspid aortic valve (BAV) is a common congenital abnormality and undergoes accelerated degenerative change and dystrophic calcification [17]. Only a minority develop ‘pure’ regurgitation. Prevalence of BAV is as high as 1–2% of the population, more common in men and a pre-existing lesion in approximately 20% of cases of IE [12]. The estimated hazard ratio (HR) for adults with a BAV, of acquiring IE up to middle age is 6.3 (CI, 3.0–13.4), with an incidence of approximately 2 per 1000 patient-years [5, 58]. According to Kiyota et al. [59], BAV carries a relative risk (RR) of 23.1 times that of a tricuspid aortic valve for acquiring IE. With aortic coarctation (AoC), the incidence of IE is <1 per 1000 patient years [12, 58]. At 25 years out, the cumulative incidence of IE in another study was 3.5% (563 pts. with median age at time of surgery, 1.9 years) [60].

7.5. Congenital aortic stenosis

Incidence of IE in congenital aortic stenosis is estimated at 2.0–2.71 per 1000 patient-years [12, 61]. Echocardiographic predictors of risk of endocarditis include AV gradient and a non-statistically significant increase in the presence of regurgitation. In the Second Natural History Study (NHS-2), Gersony et al. [55], found patients with peak gradient (PG) across the aortic valve of <50 mmHg had an IE rate of 0.45 per 1000 person-years versus 5.44 per 1000 person-years in those with gradient ≥50 mmHg. When the stenotic valve was associated with aortic regurgitation (AR), rates of IE increased from 1.98 up to 3.43 per 1000 patient-years (not statistically significant, p = 0.105) [55]. In those managed medically and with a PG < 50 mmHg, the
risk of IE was 0.27 per 1000 person-years and for patient with aortic valve replacement (AVR), follow-up rate of IE was 1.53 per 1000 person-years [55]. In a different study, the cumulative risk was 13.3% out to 25 years post-surgery (median age of surgery 7.0 years) in patients where follow-up was available. This equates to a higher annualised incidence of 7.2 per 1000 patient-years [60].

7.6. Pulmonary valve and tetralogy of Fallot

Pulmonary stenosis (PS) is usually related to congenital valve stenosis, sometimes in association with genetic syndromes. Pulmonary regurgitation (PR) due to congenital disease is mostly seen following previous repair of ToF or valvotomy [62]. Endocarditis of the PV is relatively uncommon both pre and post-surgery [55, 57, 60], except in palliative shunts [60]. In PS, a rate of 0.09 per 1000 person-years has been reported [55]. Tetralogy of Fallot carries a risk of approximately 1–2.3 per 1000 patient-years [12, 58].

7.7. Post-surgical and catheter intervention

In the Kuijpers et al. study [5], the following were noted: (i) 8 cases of IE with closed ASD, but of those, 6/8 were associated with a valve abnormality; (ii) 13 cases of IE with VSD, where 9/13 were open, and (iii) no cases of IE with PDA (83.6% were closed). A large population-based registry study of children who underwent surgical repair of congenital heart lesions reported no patient developed IE after surgical repair of PDA (620 patients, median age 2.6 years) and likewise in an ACHD population, no IE was reported [58]. The annualised risk of IE post repair of AoC has been estimated at 1.2 per 1000 patient-years [60]. Very uncommonly, early (<6 months) IE occurs after closure. Late onset IE is very rare and is usually due to delayed endothelialisation [63–65]. In fact, in a surgical follow-up study by Morris et al. [60], no children who underwent repair of an isolated secundum ASD developed IE following surgery. Small numbers were seen with primum ASD and complete AVSD. After 6 months post-surgical closure of ASD, VSD and PDA, the risk of IE is virtually eliminated. The same holds true for transcatheter closure, although with residual defects, the risk is not eliminated [52]. After definitive surgical repair of ToF, the risk is estimated at 0.7 per 1000 patient years but is much higher for a palliative shunt, at 8.2 per 1000 patient-years [60].

In a study by Rushani et al. [50], from the age of 0–6 months, unoperated cyanotic disease had an adjusted rate ratio (using ASD as a reference) for IE of 7.56, compared with the operated group at 9.22. For unoperated left-sided cardiac lesions, the rate ratio of IE was 2.35, though data was insufficient in the operated group to calculate the ratio [50].

In one study, the risk of IE was 5x increased early (<6 months) after any cardiac surgery in children [50] and 9.07x increased in adults up to 6 months after any non-valvular cardiac surgery [51]. Kuijpers et al. [5] reported valved-prosthetics in ACHD carry a hazard ratio (HR) of 17.29 (at 6 months), 15.91 (6-12 months) and 5.26 (>12 months) post-surgery. Non-valve containing prosthetics and repairs were associated with a HR of 3.34 at 0–6 months but no increase risk >6 months. The current European endocarditis prophylaxis guidelines (referred to elsewhere in this chapter) and US guidelines, accordingly recommend antibiotic prophylaxis for 6 months after complete closure of a defect with prosthetic material, regardless of whether it be percutaneously or surgically treated [57, 61].
8. Hypertrophic cardiomyopathy

8.1. Pathophysiology and diagnosis

Hypertrophic cardiomyopathy (HCM) is an inherited genetic disorder characterised by myocardial thickening. Often this is asymmetric with marked involvement of the ventricular septum. In this setting, increased gradients are generated through the left ventricular outflow tract (LVOT) and if sufficient, result in systolic motion of the anterior mitral leaflet (SAM). Repeated trauma from contact between endocardial surfaces, results in formation of plaques on the ventricular septum, at the point of contact with the MV leaflet. There are altered mechanical and haemodynamic forces acting on the MV, AV and LVOT. This predisposes to endothelial trauma and inflammation, with the potential formation of NBTE and IE at multiple sites [17].

8.2. Echocardiographic diagnosis and predictors of endocarditis risk

Modern echocardiography is readily utilised to diagnose hypertrophic obstructive cardiomyopathy (HOCM). Typical criteria include an unexplained septal thickness of ≥15 mm and LVOT obstruction as a resting or provoked gradient of ≥30 mmHg. In one study [66], the incidence of IE was 1.4 per 1000 patient-years. Echocardiographic predictors of IE risk included: (i) resting LVOT obstruction with incidence of 3.0 per 1000 patient-years, and (ii) marked left atrial dilatation (in presence of resting LVOT obstruction) with incidence of 9.2 per 1000 patient-years. Left ventricular wall thickness was not associated with increased risk [66].

There is overall conflicting data, with some studies finding IE is related to LVOT gradient and a propensity for MV infection, whilst other studies have found the contrary, with no particular relation to LVOT gradient or predilection for AV or MV [67].

9. Postinflammatory valve disease

9.1. Background and pathologic changes

The most common type of postinflammatory valve disease occurs as a sequela of rheumatic fever, leading to RHD. As discussed earlier in this chapter, the incidence has dramatically reduced in high-income countries, except in certain indigenous populations and remains a major global health burden across middle and low-income countries. In Australia, the estimated rate of ARF in young indigenous Australians aged 5–14 years is 150–380 per 100,000 person-years [68].

Rheumatic AV changes include thickening of the cusps, extending to the free margins and associated with commissural fusion. Calcification may eventually develop and occurs predominantly at the commissures and cusp margins. Concomitant changes at the MV are usual and involve thickening and retraction of the leaflets and chords along with commissural fusion. With ‘pure’ aortic regurgitation, there is cusp fibrosis with leaflet retraction. Fusion of the cusps may mimic a congenital BAV and a ‘fish mouth’ appearance of the MV on echo. Systemic lupus erythematosus and other inflammatory and autoimmune conditions can mimic rheumatic changes [16]. Rheumatic heart disease may involve all cardiac valves, but
the mitral is most commonly affected. Stenosis is more commonly present at the mitral valve and regurgitation involving the aortic [49].

9.2. Echocardiographic diagnosis of rheumatic heart disease

The revised Jones Criteria [69] for diagnosis of ARF, importantly has now incorporated Doppler echo for both acute and chronic valvulitis. In the previous guideline (1992), cardiac involvement was based on clinical auscultation. Modern-era echo has been validated for diagnosis of subclinical carditis. Echo may either help confirm or exclude carditis when a murmur is present, or it may detect subclinical carditis. The most common cardiac changes are cardiac valve involvement (valvulitis) and may be accompanied by a pancarditis with or without a myopericarditis [69].

9.2.1. Echocardiographic diagnosis: Doppler haemodynamics and 2D features

With acute rheumatic mitral and aortic valvulopathy, functional and haemodynamic changes are readily diagnosed by Doppler echocardiography. The regurgitation must be demonstrated in at least 2 views with a peak jet velocity of ≥3 m/s, a pan systolic or diastolic jet respectively and a jet length of ≥2 cm for MR and ≥1 cm for AR. Morphological changes may or may not be present early during infection [69]. The morphological change(s) seen at the MV during acute valvulitis/carditis include: (i) annular dilatation, (ii) chordal elongation/rupture, (iii) leaflet prolapse and/or (iv) beading/nodular thickening of the leaflet tips. Chronic changes of the mitral valve apparatus include: (i) thickening of the leaflets/chords, (ii) chordal fusion, (iii) restriction of leaflet motion and/or (iv) calcification [69]. Acute and chronic aortic valve changes of rheumatic valvulitis/carditis demonstrated with 2-D echo include: (i) irregular and/or focal thickening of the leaflets, (ii) leaflet retraction/restriction with or without coaptation defects and/or (iii) leaflet prolapse [69].

9.2.2. Risk of endocarditis

Incidence of IE in persons with RHD is 3.8–440 per 1000 patient-years [61]. Data published from the National Health Service in England [70], revealed a marginally lower incidence of 3.05 cases per 1000 patient-years, compared with nonrheumatic valve disease at 2.73 per 1000 patient-years in the same study. The incidence of IE in rheumatic mitral stenosis is estimated at 0.17 per 1000 patient-years. Severity of valvular haemodynamics in RHD and risk of IE is not well described.

10. Intravenous drug use

Intravenous drug use (IVDU), along with cardiac-devices, CHD and vascular access catheters, are the major risk factors for RSIE. Right-sided IE constitutes 5–10% of IE cases and approximately 90% of RSIE involves the TV [71]. Overall, IVDU use accounts for 5–10% of all cases of IE [3, 72]. The median age at time of infection is 30–40 years, not infrequently seen in patients
with human immunodeficiency virus (HIV). The majority of cases (right-sided > left-sided) are thought to involve structurally normal cardiac valves [8, 72]. Staphylococcus is the usual microorganism however infections are not infrequently polymicrobial [57]. Various fungi and pseudomonas are noteworthy for severe cases of IVDU-associated IE [8]. Interestingly, streptococci and enterococci more commonly affect left-sided valves, often with underlying structural abnormalities [73, 74].

According to Mathew et al. [75], the overall incidence of left-sided cardiac involvement was similar to right-sided IE, with a minority involving both right and left-sided valves [75]. Others have reported a predominance of right-sided lesions in patients with IVDU [72, 76]. The overall incidence of IE in IVDU is estimated at 0.7–20 cases per 1000 patient-years [74, 77]. The increased risk of IVDU patients acquiring IE is likely attributable to a multitude of factors. Proposed explanations include: (i) particulate matter injury to endothelium from substrate injection, (ii) drug-induced thrombus formation and vasospasm, (iii) immune complex deposition on valves, (iv) altered host immune function, (v) frequent exposure to high volume bacterial inoculation, (v) increased prevalence of staphylococcal skin carriage, and (vi) sympathomimetic-induced PHTN resulting in an increase in valvular regurgitation velocity and endothelial trauma. A preference for right-sided involvement of structurally normal valves may also be related to altered host and microorganism factors [71, 74, 78]. It is theorised particulate matter up to 8–10 μm in size can transit across the normal pulmonary vasculature and potentially traumatise left-sided valvular endothelium [75]. However, the relatively high prevalence of left-sided valve involvement in the IVDU cohort without apparent underlying valve disease, may not be completely explained by the above theories and warrants further research.

Transthoracic echocardiography is often very useful in IVDU patients for excluding predisposing underlying structural heart disease and providing confirmation of IE, especially for TV endocarditis. Patients with IVDU are often younger and with satisfactory acoustic windows. In addition, the TV is located anteriorly within chest, being in close proximity to the imaging transducer. The use of TOE is preferred for complicated cases of right and left-sided IE, such as periannular extension, prosthetic valves, nondiagnostic TTE, CHD and for excluding infection at other sites within the right heart, such as the Eustachian valve, atrial wall or vena cavae.

11. Prosthetic cardiac valves, devices and risk of endocarditis

11.1. Surgical valves

The estimated risk of prosthetic valve endocarditis (PVE) overall is 0.3–1.2% per patient year (3–12 per 1000 patient-years) [57]. Recent study data from the National Health Service in England [70] reported an incidence of 4.64 cases per 1000 patient-years. In a landmark early study from the 1980s, the risk for mechanical valve IE was shown to be higher in first 3 months post-surgery, whilst for porcine valves, the IE risk was higher >12 months. The cumulative risk by 5 years was not significantly different between mechanical and porcine [79].
A large study recently published, incorporating contemporary valve data, has found bioprosthetic valves do carry a higher risk for IE than mechanical valves, with a multivariable-adjusted hazard ratio of 1.65 (CI, 1.16–2.37) for early (<12 month) and 1.53 (CI, 1.25–1.86) for late (>12 months) IE. The crude incidence rates were 11.7 vs. 7 per 1000 patient-years for early IE and 6.0 vs. 4.3 per 1000 patient-years at 1–5 years (post-surgery) for bioprosthetic and mechanical valves, respectively. Similar rates were seen out to 15 years of follow-up in both groups. The overall combined incidence for PVE was 0.57% (5.7/1000) per patient-year [80]. It was suggested structural deterioration of prosthetic valves is a contributing risk factor, but this requires further investigation. Another study found a higher risk of IE with bioprosthetic over mechanical AVR, where the incidence of re-hospitalisation for IE was at 2.2% versus 1.4%, over 12 years follow-up, with adjusted hazard ratio of 1.6 (CI, 1.31–1.94). This difference was seen across all groups, except those aged 75–80 years and patients with renal failure [80].

11.2. Valve repairs

Valve repairs with prosthetic material carry a reported incidence of 4.71 cases per 1000 patient years [70]. In a pooled analysis (24 studies), recurrence of IE after mitral valve repair versus surgical replacement was 1.8% compared to 7.3% (p 0.0013), with a mean follow-up of approximately 50 months [81].

11.3. Transcatheter valves

The incidence of IE in transcatheter aortic valve replacement (TAVR) is similar to surgically placed prosthetic valves. There is no reported significant difference between self-expanding and balloon-expanding IE rates. Residual moderate or severe regurgitation was associated with higher rates of IE at 16.3 per 1000 patient-years versus 9.3 per 1000 patient-years for mild or no aortic regurgitation [82].

For pulmonary transcatheter valve (Medtronic Melody™), one study [83] reported a rate of IE of 3% per patient-year for a median follow-up of approximately 2 years. With regard to valved-conduits, the incidence of IE with RVOT homografts was lower at 0.8% per patient-year compared to Contegra-Melody conduit rate of 2.7–3.0% per patient-year. In patients with an infected Melody valve, 4/8 had a peak gradient >40 mmHg, whilst only 5/99 in the non-IE group had a similar gradient (p < 0.05) [83]. This suggests a possible increased risk of IE with residual post-procedural gradients, but numbers are insufficient and further studies are required to confirm or refute this assertion.

11.4. Device-related endocarditis

Ventricular assist devices (VADs) carry an incidence of IE of 5.8 cases per 1000 patient-years [70]. In one study investigating VAD infections, the following rates (cases per 100 LVAD-years) were found: i) all infection types –32.8 (CI, 26.7–39.9), ii) IE 1.6 (CI, 0.5–3.8) and iii) bloodstream – VAD-related, 7.5 (CI, 4.7–11.2) [84].
Implantable pacemakers (PPM) and cardiac defibrillators (ICD) have a reported incidence of IE ranging from 0.68–1.9 cases per 1000 patient-years [57, 70]. Cardiac device-related infective endocarditis accounts for 10–23% of device infections [85]. Numerous risk factors have been identified, including previous device-related infection, however information on risk related to underlying structural cardiac or TV pathology is uncertain. From the ICE-PICS data [86], 6.4% of all cases of IE were CDRIE. Over one-third of cases had associated valvular involvement, most commonly the tricuspid valve.

11.5. Recurrent native and prosthetic valve infective endocarditis

One of the most important cardiac risk factors for endocarditis is a prior history of IE. In the ICE-PCS cohort, recurrent IE occurred in 4.8% of patients, given an odds ratio of 2.8 (CI, 1.5–5.1) [87]. This is concordant with findings from other published studies with rates between 3.3 and 11.7% [88, 89]. In a recent study, the risk for recurrent IE was 14.36 per 1000 patient-years [70]. In a different study, the risk of recurrence (in patient-years) was estimated as follows: (i) history of previous IE, 7.4 per 1000, (ii) prosthetic valve surgery for native valve IE, 6.3 per 1000 and, (iii) prosthetic valve surgery for prosthetic valve IE, 21.6 per 1000 [61]. In a meta-analysis comparing biological versus mechanical valve for IE surgery, recurrence of IE in mechanical valves was 3–9% and for biological valves 7–29% [90]. Other studies have found equal rates of reinfection of bioprosthetic and mechanical valves.

Renzulli et al. [91], interestingly reported there was no association with previous perivalvular extension and recurrent risk [91]. In a study focussing on aortic homografts, Flameng et al. [92] found the recurrence rate of IE was relatively low at 7% at a mean follow-up of 8 ± 5 years. A significant downside is the high rate of structural deterioration of aortic homografts, with a rate of 40% at 10 years [92].

Shimokawa et al. [93] reviewed long term outcomes of mitral valve repair following IE in patients with prolapse and found good outcomes when compared with repair for degenerative MVP without IE. In this study, there were no recurrences of IE [93]. In another meta-analysis, comparing MV replacement with MV repair in the setting of IE, the 5 year risk of recurrent IE was favourable in the repair group with OR 0.39 (0.10–1.58) [94].

12. Conclusion

The three main categories of cardiac disease predisposing to infective endocarditis are degenerative valve disease, congenital heart disease and less commonly in high-income countries, rheumatic heart disease. The changing epidemiology has been associated with an ageing population, increased prevalence of prosthetic valves, devices and shunts, and health-care exposure. This chapter has outlined the underlying pathology, risks and echocardiographic predictors for IE associated with a selection of lesion-specific cardiac pathologies. The chapter also addressed the observation of structurally ‘normal’ cardiac valves accounting for a rising proportion of IE cases. Whether this relates to microorganism virulence, host factors, early structural and
functional changes associated with degenerative valve disease, or a combination of all of the above, is unproven. Only further focused research using modern-era high resolution imaging and clinicopathological correlation, will provide new insight into this interesting question.

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