Heart Murmur in a Child

Case Study and Commentary, David A. Danford, MD

DR. LIANG:

Most primary care physicians and providers who see children have experienced auscultation of a heart murmur.[1] Although heart murmurs are common in children, significant issues must be addressed to ensure that these pediatric patients and their parents are not overwhelmed or given a false basis for anxiety regarding the implications of a discovered heart murmur in a child.[2]

First, as noted in this case study, most children with a heart murmur do not have significant heart disease.[3,4] Unfortunately, diagnostic accuracy by primary care physicians is variable. In one study, more than 60% of murmurs referred for subspecialist pediatric cardiologist assessment were deemed to be innocent murmurs that did not require further evaluation.[5] This finding supports the need for primary care physicians to be educated regarding the extent of innocent murmurs in pediatric patients and strategies for evaluating them.

Additional awareness regarding the incidence and prevalence of pediatric heart murmurs would have a significant impact upon the health care financial system. Many primary care physicians refer pediatric patients with a detected murmur for ultrasound evaluation. It has been shown, however, that direct referral of these patients for echocardiography is an extremely expensive means by which to determine the patient's diagnosis.[6] Furthermore, if the patient is referred to an adult echocardiographic facility, as is often the case, the resulting diagnostic information may be suspect: pediatric echocardiograms performed at adult echocardiographic practices were found to be unnecessary in 30% of cases, to be of inadequate quality for diagnostic purposes in 32% of cases, and, most disturbingly, to present an erroneous impression regarding presence of cardiac pathology in an astounding 32% of cases.[7] However, using the expertise of a pediatric cardiologist in combination with echocardiogram does result in a cost-effective approach to diagnosing cardiac disease in children if a primary care diagnosis is not made.[8]

Newer methods have been reported to assist in the diagnosis of cardiac disease in pediatric patients. DeGroff and colleagues[9] have reported the use of neu-ral network computer programs and electronic stethoscope to diagnose heart murmurs in pediatric patients. Using this technology, these investigators were successful in accurately distinguishing between abnormal heart murmurs and innocent heart murmurs with an incredible 100% sensitivity and 100% specificity in patients aged 1 week to 15 years. Clearly, this technology can be of great assistance in quickly and accurately diagnosing children with a murmur.

The presence or discovery of a murmur in the pediatric patient is a common occurrence. Primary care physicians should be attentive to these findings, and assess them with care, using clinical signs and symptoms as well as technology and judicious referral. By doing so, they will be able to assist their patients and, hopefully, allay fears of family members regarding these findings while also containing costs in the diagnostic work-up of these patients.

DR. DANFORD:

Cardiac murmur is frequently recognized in healthy children, but it also can be the presenting feature in many forms of congenital heart disease, including regurgitation or stenosis of heart valves or left-to-right shunt lesions at the atrial, ventricular, or great arterial levels. Careful examination reveals innocent systolic murmurs in as many as 72% of all school-age children.[10] A high prevalence of innocent murmur also has been documented in infants and neonates.[11] Seven types of innocent heart murmurs are reported in children, including Still's murmur,[12–14] innocent pulmonary flow murmur,[15–17] innocent pulmonary branch murmur of infancy,[18] supraclavicular bruit,[19] venous hum,[20] mammary souffle,[21] and cardiorespiratory

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murmur.[22] Generally, the clinical history and physical examination are diagnostic for these murmurs.

Congenital heart disease is much less prevalent than innocent murmur, occurring in only about 0.8% of live births,[23] but the natural history of many common congenital cardiac defects can be one of progressive limitation and premature death. The primary care physician, therefore, very frequently faces the challenge of distinguishing between the relatively rare but important pathologic murmur and the ubiquitous innocent murmur. Failure to diagnose heart disease is unacceptable because current treatments can dramatically improve outcomes. On the other hand, the costs of embarking nonselectively on an aggressive laboratory and/or subspecialty evaluation for as much as 70% of the pediatric population would be staggering.[6] This article discusses diagnostic strategies that allow for timely identification of important congenital cardiac defects while at the same time controlling costs.

CASE STUDY
Initial Presentation

A 5-year-old boy is brought to the office by his mother for a health care maintenance visit in advance of the start of kindergarten. The child has been seen in the office regularly since birth for health care maintenance and immunizations and, occasionally, for minor acute infectious respiratory ailments. At this visit, the physical examination reveals a systolic murmur for the first time.

- **What is required to conclude that this child has an innocent heart murmur?**

Three findings are necessary to make the diagnosis of innocent murmur in a child. First, the examiner must recognize with confidence the classic auscultatory features of a specific innocent murmur. A summary of characteristics that help identify these murmurs is presented in **Table 1**. Second, a careful, cardiac-specific history must reveal no compelling evidence of heart disease. Third, a careful, cardiac-specific physical examination (beyond simple auscultation of the heart) must reveal no compelling evidence of heart disease. Laboratory testing is not necessary to make the diagnosis of innocent murmur in the vast majority of cases.[4,8]

- **What elements of the history are important in the evaluation of heart murmur?**

Family History and Past Medical History

Clues to heart disease should be sought in the family history and the past medical history. A positive family history for congenital heart defect will raise the level of suspicion of pathologic heart murmur because of the tendency for congenital heart defects to cluster in certain families.[24] Moreover, in the course of taking the history, it is important to assess whether the child's past medical history includes prior diagnosis of a genetic condition known to be associated with congenital heart disease, such as aneuploidy (eg, Trisomy 21[25]) or other dysmorphic syndromes (eg, VACTERL[26]). As a matter of routine, physicians evaluating a child with a heart murmur should inquire about any major congenital defects of other organ systems because it is well known that many patients have cardiac anomalies as part of a constellation of birth defects, even if the constellation does not represent an identified genetic syndrome.[27,28] Because of the known association between connective tissue abnormalities and acquired cardiovascular disease, one should view a cardiac murmur in a child known to have Marfan syndrome with a high level of suspicion.[29,30] Specific inquiry about prior diagnosis of connective tissue disorders is appropriate. Finally, there are myriad inborn errors of metabolism that predispose to cardiomyopathies,[31] some of which may produce murmurs of valvular insufficiency or dynamic left ventricular outflow obstruction. Therefore, learning that a patient with a murmur also has an inborn error of metabolism greatly changes the context of the murmur evaluation. The physician should also ask if there has been any prior diagnosis of a cardiovascular condition, such as a past episode of rheumatic fever, a past episode of Kawasaki disease, or known cardiac arrhythmia.

Cardiac-Specific Issues in the Current History

Some innocent murmurs have a specific time course over which they appear (eg, the innocent pulmonary branch murmur of infancy[32]), and some become prominent primarily at times of high cardiac output (eg, innocent pulmonary flow murmur, Still's murmur[33]). Accordingly, inquiry into the time course over which the murmur has been noted and the circumstances under which it has been observed can be very revealing. Growth history is important because many forms of congenital heart disease compromise the patient's rate of growth.[34] Generally, patients with compromised growth have large left-to-right shunts that produce the dual burdens of increased metabolic demands and poor oral intake. Older children may manifest similar types of heart disease by exercise intolerance, easy fatigue, and diaphoresis either at rest or on exertion. Respiratory complaints may include chronic cough, asthma-like symptoms, dyspnea on exertion, and poor feeding, especially in infants unable to simultaneously breathe heavily and suck and swallow. Inquiry

Table 1. Characteristics of Innocent Murmurs

Type of Innocent Murmur	Timing, Location	Character, Pitch	Helpful Maneuvers	Common Clinical Setting	Cause
Still's	Systolic ejection; slightly lateral to left lower sternal border	Vibratory, musical, like a low-pitched stringed instrument	Diminishes in intensity with inspiration, sitting up, or standing	Although it can occur at any age, it is particularly common in young school-age children, often detected at the kindergarten physical; it is accentuated by fever or other high cardiac output states	Harmonic vibrations of the left ventricular outflow tract
Pulmonary flow	Systolic ejection; left upper sternal border	Low-intermediate pitch; non-harmonic, non-harsh	Diminishes in intensity with inspiration, sitting, or standing	Common in all pediatric age groups, particularly infants and preschool children; accentuated by fever or other high cardiac output states	Minor degrees of turbulence in the right ventricular outflow tract and main pulmonary artery in the absence of disease of these structures
Pulmonary branch murmur of infancy	Systolic ejection; left and right upper sternal border with strong radiation to axillae and back	Intermediate pitch; non-harmonic, non-harsh	None	Often first noted at about 2 weeks of age, it is especially common in premature infants; disappears in the first several months	Physiologic pulmonary branch turbulence due to size disproportion of main pulmonary artery and right and left branches
Venous hum	Continuous; right infraclavicular, less commonly on left or bilateral	Low-intermediate pitch; "machinery-like"	Disappears with supine position or with pressure on jugular vein	Common throughout childhood	Physiologic turbulence of normal superior vena cava flow
Supraclavicular bruit	Systolic ejection; base of neck, right, left, or bilateral	Intermediate pitch; non-harmonic, non-harsh	Diminishes with neck extension with shoulders thrown back	School-age children	Minor physiologic turbulence in normal brachiocephalic arterial origins
Cardiorespiratory	Inconsistent timing and location; often at the cardiac apex	Cooing	May disappear when patient holds breath	School-age children	Technically this is a breath sound, arising from variable cardiovascular compression of an airway
Mammary souffle	Usually continuous, but may be systolic only; right, left or bilateral mid to lower sternal border	Low-intermediate pitch; "machinery-like"	Disappears with firm pressure with stethoscope	Pregnant or lactating women	Turbulence in engorged arteries and veins carrying high volume flow to and from the breasts

concerning these symptoms of pulmonary edema due to large volumes of pulmonary blood flow and/or left heart failure is a central part of cardiac-specific history taking for pediatric heart murmur. Occasionally, patients with heart disease capable of producing a murmur will have associated cardiac arrhythmias. With this in mind, the physician should ask about dizziness, syncope, palpitations, and chest pain.

Case Patient—Limited Cardiac History

This 5-year-old boy has no history of heart murmur. There has been no dyspnea, cough, wheezing, or other chronic or recurrent respiratory symptoms. He has had no trouble keeping up with his peers on the playground. There have been no complaints of chest pain, dizziness, or syncope. He has grown well and met all his developmental milestones appropriately. He has no known disease of other organ systems and was not born with any known malformation syndrome, connective tissue disorder, inborn error of metabolism, or chromosomal anomaly. The patient's mother recalls that her brother had a heart murmur as a child, but she believes it resolved. She says there is no family history of specifically diagnosed congenital heart disease.

- **What elements of the physical examination are required to evaluate this murmur?**

Cardiac-Specific Issues in the Physical Examination

Physical examination in this setting must include careful auscultation of the murmur with attention to timing, location, radiation, pitch, intensity, character, and alterations in the murmur with changes in posture. Furthermore, one must evaluate the character of heart sounds, listen closely for accompanying clicks, gallops, and rubs, and palpate the precordial impulses and the pulses in the upper and lower extremities. Vital signs must be measured, including heart rate and regularity; respiratory rate, with observation for cardinal features of respiratory distress (ie, grunting, flaring, retractions); blood pressure of the upper and lower extremities; and height and weight plotted on a growth chart. The patient's general appearance must be observed for features suggestive of dysmorphic syndrome or chromosomal abnormality, distress of any kind, cyanosis, pallor, diaphoresis, and abnormalities of peripheral perfusion. The respiratory examination should include evaluation for chest deformities as well as auscultation for adventitial sounds (rales, wheezes, rhonchi, pleural rubs) and for discrepant breath sounds on the right versus left sides. The gastrointestinal examination should include palpation for the loca-

tion of the liver (abdominal situs), the size of the liver and spleen, and the presence of ascites.

Certain characteristics of heart murmurs should raise suspicion that they are not innocent. For example, the continuous murmur of patent ductus arteriosus[35] will not disappear in the supine position like the venous hum will. Furthermore, innocent murmurs generally do not have the pansystolic timing observed in cases of ventricular septal defect[36] or mitral regurgitation.[37] While diastolic flow rumble and abnormal second heart sound are frequently recognized in atrial septal defect,[38] these are not features of innocent murmur. Ejection clicks, often identified in association with pulmonary valve stenosis[39] and aortic valve stenosis,[40] are absent in the examination of the normal heart. It is not surprising, therefore, that pansystolic murmur, loud murmurs (grade 3 or higher), harsh quality, left upper sternal border location, and murmurs associated with early- or mid-systolic clicks or an abnormal second heart sound all have been found to have an independent association with the discovery of heart disease.[8] Other authorities suggest that all diastolic murmurs, late systolic murmurs, continuous murmurs (that do not disappear with changes in posture or firm stethoscope pressure), and murmurs accompanied by other abnormal cardiac findings should be considered pathologic until proven otherwise.[1]

Case Patient—Limited Cardiac Physical Examination

The patient has a normal appearance of a healthy 5-year-old boy, with height and weight plotting at the 75th and 80th percentiles, respectively, for age. The heart rate is 95 bpm and regular. Respirations are 20 breaths/min and not labored. Blood pressure is 95/55 mm Hg in the right arm and 102/60 mm Hg in the right leg. The chest is without deformity, and the breath sounds are clear and equal bilaterally. The precordium is without abnormal impulse. The first and second heart sounds (S_1 and S_2) are probably normal, but the physician is somewhat uncertain if there is abnormal splitting of S_2. Also, the physician is uncertain whether there is an early systolic ejection click present or if this is merely a split S_1. There are no gallops. A 2/6 low-to-medium pitched nonvibratory systolic ejection murmur is heard well in the third intercostal space at the left sternal edge. However, the murmur is also audible at the right sternal edge and faintly in the back; the physician is uncertain of the precise location of its maximal intensity. The murmur does not change when the patient sits up. There are no diastolic murmurs. Pulses are normal in intensity and equal in the arms and in the legs. Hepatosplenomegaly, ascites, or peripheral edema are not present.

Table 2. Common Cardiac Conditions Presenting as Murmur

Cardiac Lesion	No. of Patients	New Patients with Heart Disease Who Have Cardiac Lesion, %*	Mean Age at Diagnosis (25th, 50th, 75th Percentiles), y	Male Sex, %
Ventricular septal defect—small muscular	239	31.9	1.23 (0.04, 0.17, 0.83)	44.8
Pulmonary valve stenosis	140	18.7	0.96 (0.08, 0.25, 0.75)	43.6
Aortic valve disease	120	16.0	5.63 (0.94, 4.00, 10.5)	68.9
Ventricular septal defect—large and/or not muscular	87	11.6	0.44 (0.05, 0.12, 0.23)	46.0
Atrial septal defect	79	10.5	1.66 (0.38, 0.75, 1.33)	31.6
Patent ductus arteriosus	58	7.7	1.51 (0.04, 0.23, 1.37)	51.7
Mitral valve disease	39	5.2	6.90 (1.27, 5.50, 13.0)	38.5
Coarctation of the aorta	26	3.5	3.93 (0.71, 2.25, 5.25)	65.4
Subaortic stenosis	16	2.1	6.37 (3.00, 4.50, 9.00)	62.5
Tetralogy of Fallot	10	1.3	0.03 (0.01, 0.015, 0.06)	60.0
Atrioventricular septal defect	9	1.2	3.43 (0.16, 2.25, 6.50)	44.4

Data from Danford DA. Role of echocardiography in the initial assessment of heart murmurs. Pediatr Ultrasound Today 1999;4:57–80; table updated Nov 2001.

*Sum is greater than 100% because patients can have more than 1 lesion.

- **Can a clinical diagnosis of innocent murmur be made in this patient?**

A limited cardiac-specific history has been taken, and this failed to identify any historical features to suggest heart disease in this patient. Most of the cardiac-specific physical examination also is reassuring. However, because of the lingering uncertainties about the location of the murmur, the characteristics of S_2, and the presence or absence of an ejection click, the physician cannot claim to unequivocally recognize the features of a particular innocent murmur (based on the list in Table 1). The clinical diagnosis of innocent murmur cannot be made at this point.

- **If this is not an innocent murmur, what is the differential diagnosis?**

A prospective study evaluated the characteristics of outpatients referred for echocardiography from a pediatric cardiology outpatient clinic[41–44]; the most common cardiac conditions encountered, ages at diagnosis, and sex distribution by lesion from this study are listed in **Table 2**. Although the physical examination is somewhat ambiguous in this patient, an ejection click, if present, would suggest either pulmonary valve stenosis or aortic valve stenosis. The murmur in aortic stenosis classically would be more prominent at the right upper sternal border and might transmit well to the neck. None of these findings were identified in this case. The description of this murmur's probable left sternal border location and possible transmission to the back fits better with a main pulmonary arterial origin for the murmur, such as would be present with pulmonary valve stenosis.

If the click is actually absent, aortic or pulmonary valve disease is still possible but distinctly less likely. Innocent pulmonary flow murmur is possible, and subaortic membrane would be unusual but is possible. Atrial septal defect generally produces a systolic ejection murmur of pulmonary origin but usually is associated with a diastolic flow rumble at the left lower sternal border and a widely split S_2 that does not vary with respirations. The examination suggested the possibility of a split S_2 but did not mention a diastolic flow rumble. Flow rumbles can, however, be subtle findings. Whatever this murmur represents, it does not appear to be a very significant hemodynamic burden for the heart since the patient is asymptomatic and does not have increased left or right ventricular precordial impulses.

- **What approaches to diagnosis of heart murmur are available?**
- **Which should be used in this patient?**

Diagnostic Options

In general, when faced with uncertainty about a diagnosis, a primary care physician needs to gather more data, usually with laboratory testing, or by seeking a specialty or subspecialty opinion. For heart murmur, the laboratory testing considered is usually chest radiography,

Table 3. Methods to Discriminate Ventricular Septal Defect (VSD) from Innocent Murmur

Diagnostic Modality	Ventricular Septal Defect			Innocent Murmur		
	Possible Findings	Advantages	Disadvantages	Usual Findings	Advantages	Disadvantages
ECG	RVH LVH BVH	Inexpensive	Insensitivity: will likely be normal in small VSD Nonspecificity: abnormal findings are not unique to VSD	Normal	Inexpensive	False-positive findings will provoke anxiety and require further evaluation
Chest radiograph	Cardiomegaly Increased pulmonary vascular markings	Inexpensive	Insensitivity: will likely be normal in small VSD Nonspecificity: abnormal findings are not unique to VSD	Normal	Inexpensive	False-positive findings will provoke anxiety and require further evaluation
Echocardiogram	VSD	Definitive for anatomic location of VSD Good indication of VSD size and pulmonary arterial pressure	Expensive	Normal	Usually definitive and immediately available	Expensive Can be misleading if done in a lab unaccustomed to examining children Can promote cardiac nondisease if results are not carefully presented
Pediatric cardiology consultation	Clinical findings highly suggestive of VSD	Inexpensive Opportunity for discussion of implications with patient/ family	Insensitivity: occasional failures to recognize small VSD Nonspecificity: occasionally results in echocardiography when the heart is actually normal	Clinical findings highly suggestive of innocent murmur	Inexpensive Opportunity to reassure family	Sometimes not immediately available Will, on rare occasions, fail to diagnose minor heart disease

BVH = biventricular hypertrophy; ECG = electrocardiogram; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy.

electrocardiography, or echocardiography. The subspecialty opinion would be available through pediatric cardiology consultation. **Table 3** highlights some of the advantages and disadvantages of each of these approaches for the 2 most common examples of heart murmur in children, innocent murmur and ventricular septal defect. Although inexpensive, the chest radiograph and electrocardiogram (ECG) are neither sensitive enough nor specific enough to be helpful to the generalist trying to distinguish ventricular septal defect from innocent murmur.[45,46] The echocardiogram is diagnostically definitive, but this modality would be expensive for general application to large numbers of patients who turn out to have an innocent murmur.[6]

Pediatric cardiology consultation to evaluate the not-clearly-innocent murmur screens out most innocent murmurs, and when ventricular septal defect is present, an echocardiogram can be arranged to define its anatomic location and physiologic significance.

Electrocardiogram. Similar to the observations with ventricular septal defect, the electrocardiogram has limited sensitivity for the other common forms of congenital heart disease that present with murmur.[47–50] Because many children with significant heart disease will have a normal ECG, it is hazardous to conclude from a normal ECG that a murmur is innocent. Some authorities point to advantages of the ECG as an integral part of the evaluation of murmur in children.[51] A further

argument may be made that the incidental discovery of electrocardiographic abnormalities like Wolff-Parkinson-White syndrome or prolonged QT interval during screening could be very valuable in individual cases. However, large clinical series of children undergoing evaluation for heart murmur in the pediatric cardiology clinic have suggested that the expert clinical examination for evaluation of a murmur is not enhanced by the performance of an ECG.[4,8,52] Despite its low cost, the ECG is unlikely to be of help distinguishing the pathologic murmur from the innocent one in the primary care outpatient setting.

Chest radiography. Like the ECG, radiography findings in congenital heart disease have poor sensitivity, with many of the classic radiographic features appearing late in the clinical course.[47–49,53] False-positive cardiomegaly is relatively common in young children due to a large thymus or poor inspiratory effort, and this further degrades the value of the test. Although some support the use of chest radiograph as a routine component of the pediatric cardiologist's evaluation of heart murmur,[51] investigators have had difficulty in showing an advantage to this approach.[4,8,52] Radiography should not be routine in the primary care physician's initial evaluation of heart murmur.

Echocardiography. Echocardiography is an exquisitely accurate means for diagnosis of congenital heart disease when technologists trained and practiced in the pediatric examination perform the test using equipment suitable for children and when the test is interpreted by pediatric echocardiographers.[54] Evidence is accumulating, however, that the accuracy of echocardiography for children is reduced when it is performed in laboratories geared toward adult echocardiography and interpreted by physicians unfamiliar with imaging congenital heart disease[7,55] Unfortunately, this modality is quite expensive relative to any of the modalities discussed thus far, and for this reason is poorly suited to serve as a screening tool. Using echocardiography as a first-line diagnostic test after the primary physician appreciates a heart murmur is an expensive strategy. In 1993, the marginal cost of echocardiograpy to the patient/payer relative to the cost of pediatric cardiology consultation and subsequent echocardiography if necessary was more than $250/murmur evaluation.[6] Occasionally, important congenital cardiac defects are identified echocardiographically even when the pediatric cardiologist believes that pathology is quite unlikely.[56] However, it has recently been estimated that a strategy of echocardiography for all childhood heart murmurs would detect heart disease at a marginal cost of $158,000 for each case that would have escaped recognition by a pediatric cardiologist.[57]

Pediatric cardiology consultation. Probably because of training and practice, the experienced pediatric cardiologist offers greater diagnostic sensitivity and specificity for the diagnosis of congenital heart defect than does the generalist.[58,59] Measured against the anatomic standard of echocardiography, the pediatric cardiology specialty examination carries sensitivity and specificity of approximately 95% for discriminating heart disease from innocent murmur.[4,60,61] Ordinarily, consultation is available in a timely fashion, and the cost is relatively small, enhancing the appeal of using the pediatric cardiologist as a "second screen." This strategy is less appealing if the pediatric cardiologist is at a great distance, especially if the murmur is in a neonate who must have a medically supervised transport to complete the consultation. The advantages of pediatric cardiology consultation are limited if the cardiologist is not selective in the use of expensive tests, such as echocardiography.[6] In the case patient, the approach of choice is a consultation with a pediatric cardiologist, who will then decide if echocardiography is indicated.

Case Patient—Referral to Pediatric Cardiologist

An outpatient evaluation by a pediatric cardiologist is arranged. Reexamination by this physician confirms a 2/6 low-to-medium pitched systolic ejection murmur maximal at the left upper sternal border with faint transmission to the back. The S_2 splits prominently enough so that the physician can easily discern the 2 components, but the splitting varies physiologically with respiration. An ejection click is indeed present at the left midsternal border. The physician makes a provisional diagnosis of mild pulmonary valve stenosis and arranges for echocardiography examination.

- **What is the rationale for echocardiography in this patient?**

The sensitivity and specificity of pediatric cardiologists' clinical diagnosis of pulmonary valve stenosis are good but not perfect—73% and 82% in a recent report.[42] Therefore, echocardiography serves 2 purposes: to confirm that pulmonary valve stenosis is in fact the true diagnosis, and to assess the severity of obstruction.

- **What are the risks for adverse outcomes in children with a heart murmur?**
- **What implications do these risks have for ongoing management?**

Common Shunt Lesions

Ventricular septal defect, atrial septal defect, and patent ductus arteriosus are associated with

Table 4. Natural History and Risks with Common Shunt Lesions

Defect	Symptoms or Impairment	Potential for Spontaneous Improvement or Resolution	Endocarditis Risk	PVOD Risk
VSD, small	Generally none	May close spontaneously (muscular defects more likely to close than others), especially before age 2 years	Yes	No
VSD, moderate	May have none, but may have failure to thrive and chronic respiratory symptoms	Can diminish in size, and spontaneous closure is possible	Yes	No
VSD, large	Chronic respiratory symptoms and failure to thrive are common	Spontaneous decrease in size or even closure is possible, but severity of symptoms and risk of pulmonary vascular disease often dictates an intervention before this can happen	Yes	Yes
ASD	Usually none in early childhood, but more and more report fatigue, dyspnea, and palpitations with advancing age Symptoms more common, more severe, and occur at an earlier age with larger ASD	Spontaneous closure of secundum ASD is possible, but uncommon, especially after age 2 years ASD in other locations is not reported to close spontaneously	No	Yes, but less likely, and usually at an older age than with large VSD
PDA	Usually none with small PDA, but chronic respiratory symptoms and failure to thrive are common in infancy with large PDA	Spontaneous closure after 6 months of age would not be expected	Yes	Yes with large PDA and pulmonary hypertension. No with small PDA
AVSD, complete	Chronic respiratory symptoms and failure to thrive are common	No	Yes	Yes
AVSD, partial	As with larger secundum ASD (above)	No	Yes	As with larger secundum ASD (above)
Tetralogy of Fallot	Can have respiratory symptoms early, but these diminish with time Cyanosis may be present early, tends to be progressive	No	Yes	No*

AR = aortic regurgitation; AS = aortic stenosis; ASD = atrial septal defect; AVSD = atrioventricular septal defect; LV = left ventricle; MR = mitral regurgitation; PDA = patent ductus arteriosus; PS = pulmonary stenosis; PVOD = pulmonary vascular obstructive disease; RA = right atrium; TR = tricuspid regurgitation; VSD = ventricular septal defect.

*Except in the unusual circumstances of associated large aorticopulmonary collateral arteries or after the surgical placement of a large systemic-to-pulmonary arterial shunt.

well-defined risks for adverse outcome, including chronic respiratory symptoms and failure to thrive attributable to pulmonary overcirculation.[22,45,46,62,63] Some patients are also at risk for bacterial endocarditis, irreversible pulmonary vascular obstructive disease (Eisenmenger's syndrome), and emergence of other hemodynamically important cardiac abnormalities.[64–66]

The natural history and risks of these conditions are summarized in **Table 4**.

Management. Because all of the common left-to-right shunt lesions (eg, ventricular septal defect, atrial septal defect, patent ductus arteriosus) except for isolated secundum type atrial septal defect are believed to carry risk for bacterial endocarditis,[67] the patient and family

Potential for Other Complications

None with muscular VSD

Small perimembranous VSDs will occasionally develop important subAS, AR, subPS, and/or direct LV to RA shunt

Small subarterial VSDs will usually develop prolapse of the sinus(es) of Valsalva into the VSD, with progressive aortic valve distortion and AR

As with small VSD (above)

As with small VSD (above)

May represent a risk for systemic embolization (stroke), especially if atrial septal aneurysm is present

Occasional association with progressive mitral prolapse and regurgitation

Atrial arrhythmias are increasingly frequent with advancing age

PDA can be a dynamic structure in some patients, demonstrating a variable degree of shunt over time

Progressive MR, TR, and subAS

Progressive MR, TR, and subAS

Progressive PS and subPS can predispose to hypercyanotic episodes

Chronic hypoxemia predisposes to polycythemia, stroke, and brain abscess

Progressive TR and right heart failure occur late

should be educated regarding use of antibiotics for dental and surgical procedures when any of these conditions is diagnosed. Although diuretics, afterload-reducing agents, and digoxin are commonly used in the initial management of the symptomatic child with a large left-to-right shunt,[68,69] definitive management generally is surgical or transcatheter obliteration of the shunt.

Although concurrently controlled studies to demonstrate the superiority of surgical or transcatheter closure over the natural history or pharmacologically modified natural history will likely never be accomplished, the low surgical risks and benign postoperative course in the modern era[70–73] do appear to compare favorably with the natural history of common shunt lesions.[66,74,75] Early intervention is key for conditions likely to produce pulmonary vascular obstructive disease. With minor left-to-right shunts through small defects, the case for surgical or transcatheter intervention is far less compelling. Patients with small defects in the muscular ventricular septum, for example, are far better served by observation, reassurance, and antimicrobial prophylaxis against bacterial endocarditis during times of risk.[75]

Common Valvular and Obstructive Lesions

A well-known set of risks also is associated with the commonly encountered valvular and obstructive lesions such as pulmonary stenosis, aortic stenosis, and coarctation of the aorta. Discovery of such lesions is important because, even if mild, they represent indications for prophylaxis against bacterial endocarditis.[65,67] In addition, some of these patients are at risk for ventricular failure, valvular regurgitation, arrhythmias, and sudden death.[49,76] Although most cardiac valve disease in children deteriorates hemodynamically with time or is static at best, mitral valve prolapse appears to be an exception. Auscultatory features of prolapse can, for reasons not well understood, disappear in a significant proportion of patients over a period of years.[77,78] The natural history and risks associated with valvular and obstructive conditions are listed in **Table 5**.

Management. Relief of coarctation of the aorta is believed to reduce the incidence of early congestive heart failure and the potentially devastating complications of chronic upper body hypertension.[79] Surgical repair is therefore usually recommended upon diagnosis; however, there has been recent enthusiasm for balloon and/or stent aortoplasty.[80]

The natural history of severe pulmonary valve disease is, in all likelihood, favorably impacted by relief of obstruction by balloon pulmonary valvuloplasty. Because transcatheter relief of pulmonary stenosis is quite effective and long lasting in most instances, surgical valvotomy or valvectomy has fallen out of favor as a first-line approach for treatment of important pulmonary stenosis.[81] Mild pulmonary valve stenosis has such a favorable natural history that surgical or transcatheter intervention to relieve it is generally not believed to be worth the admittedly small risks.[82] Evidence is not strong to

Table 5. Natural History and Risks with Common Valvular and Obstructive Lesions

Defect	Symptoms or Impairment	Potential for Spontaneous Improvement or Resolution	Endocarditis Risk	Ventricular Failure Risk	Potential for Other Complications
Pulmonary stenosis	Generally none if mild or moderate PS in children; progressive fatigue, exercise intolerance, palpitations with more severe PS among older patients	None	Yes	Greater degrees of obstruction over longer periods of time are associated with RV failure	RV hypertrophy and dilation may pose risk for arrhythmia, and progressive tricuspid annular dilation and TR
Aortic stenosis or subaortic stenosis	Generally none if mild or moderate AS in children; angina, exercise intolerance, palpitations, syncope and sudden death with severe AS	None	Yes	Greater degrees of obstruction over longer periods of time are associated with LV failure	LV ischemia during times of peak demand poses risk for ventricular arrhythmia; progressive AR is common
Coarctation of the aorta	If obstruction is not severe, freedom from symptoms early in life is the rule; angina, exercise intolerance, palpitations, syncope, and sudden death can develop later	None	Yes	Greater degrees of obstruction over longer periods of time are associated with LV failure	Stroke; premature atherosclerotic disease associated with hypertension; deterioration of the associated bicuspid aortic valve (AS or AR); ventricular arrhythmias
Mitral valve prolapse	Many are asymptomatic; some with chest pain, fatigue, palpitations, and dizziness often not directly related to hemodynamics	Yes, both the auscultatory and echocardiographic features of prolapse disappear spontaneously over time in a significant proportion of cases	Yes, if associated mitral regurgitation is present	LV failure only occurs in extraordinary cases with severe MR	Severe MR may predispose to ventricular or atrial arrhythmias; embolic stroke occasionally reported

AR = aortic regurgitation; AS = aortic stenosis; LV = left ventricle; MR = mitral regurgitation; PS = pulmonary stenosis; RV = right ventricle; TR = tricuspid regurgitation.

support either aggressive intervention or watchful waiting with moderate pulmonary valve stenosis, but current practice is to intervene for patients with a transvalve peak pressure gradient in excess of 40 mm Hg.[83]

With a greater tendency for mild disease to progress to severe[84] and a greater risk for life-threatening complications among those with severe valve disease, ongoing regular follow-up of children with mild aortic valve disease is recommended.[75] Balloon aortic valvuloplasty for moderate or severe aortic stenosis should be considered palliative rather than curative, as there is a high likelihood that the aortic valve will eventually restenose or develop important degrees of regurgitation.[85] Nonetheless, it is widely believed that relief of moderate-to-severe aortic stenosis provides advantages over the natural history,[76] and balloon valvuloplasty offers comparable hemodynamic results to surgical valvotomy without the disadvantages of sternotomy.[85] Surgical valvotomy or valve replacement is generally considered when balloon valvuloplasty is ineffective in relieving severe aortic stenosis, or when enough aortic regurgitation develops to raise concerns for left ventricular failure in the long term. Like balloon aortic valvuloplasty, surgical valvotomy is generally only palliative.[85] All surgical aortic valve replacement procedures carry significant risks for long-term complications and the all-too-frequent need for further intervention. Mechanical valves require anticoagulation (with the attendant risks) for the prevention of thrombosis and embolism.[86] Homograft valves implanted in the aortic position tend to calcify and deteriorate rapidly in children and adolescents.[87] Currently very popular, the Ross procedure uses the patient's own pulmonary valve as an autograft in the aortic position and employs a homograft replacement in the pulmonary position, where homograft durability is better compared to the aortic position.

Even the Ross procedure, unfortunately, is associated with some incidence of late deterioration of the autograft, or the homograft, or both.[88] Therefore, aortic valve replacement, by whatever means, is reserved for those patients in whom other effective means of treatment have been exhausted and whose valve disease is severe enough that the natural history would likely compare poorly with the postsurgical history.

Nondisease

Although not generally considered a risky condition in the classic sense, innocent murmur carries the peculiar risk of cardiac nondisease. The detection of a cardiac murmur, even though the majority of school age children have one, provokes significant parental anxiety.[89,90] The specter of possible heart disease in a child can be extremely burdensome for the child and the family. The child can be inappropriately "protected" from the normal activities of childhood by the family when the possibility of congenital heart disease remains a concern. Such observations prompted Bergman and Stamm[91] to coin the term "cardiac nondisease" in 1967 to describe the phenomenon. Cardiac nondisease remains a risk for children with innocent murmur in the current era, as noted by McCrindle et al[92] and Young,[2] who discovered that there was persistent concern about heart disease among the families of 10% to 17% of patients after the diagnosis of innocent murmur was made in the pediatric cardiology clinic. Greater levels of parental understanding of murmurs, however, appear to correlate with greater relief of anxiety after pediatric cardiology consultation.[89]

Management. As discussed, the discovery of an innocent heart murmur in a child is not always free from adverse consequences; however, the physician can take steps to reduce the consequences. The admonition of Friedman[93] published more than a quarter of a century ago remains true today:

> The physician must make clear to the patient with an innocent murmur that there is no need for systematic long-term cardiac supervision, antistreptococcal prophylaxis against rheumatic fever, or antibiotic prophylaxis against bacterial endocarditis. The patient and family must understand that the murmur will play no role in the prognosis of the patient even in the remote future, so there is no need for further cardiac evaluation or for restriction from any specific physical activities because of the murmur.

Physicians must convey these messages effectively to patient and family so that the child's quality of life does not suffer due to inappropriate lifestyle restrictions imposed for cardiac nondisease.

Case Patient—Echocardiography Evaluation and Diagnosis

Echocardiography in the patient shows a minimally thickened pulmonary valve with minor restriction of systolic excursion at the tips, and accelerated main pulmonary arterial systolic flow velocity to 2.5 m/s, consistent with a peak systolic pressure gradient of 25 mm Hg. The right ventricle is neither hypertrophied nor dilated. The remainder of the examination is normal. The physician informs the patient and family of the diagnosis of mild pulmonary valve stenosis and its favorable natural history. The physician reassures them that no restrictions are necessary for participation in athletics. Instructions are given for the appropriate use of antibiotic prophylaxis against bacterial endocarditis for dental or surgical work. Follow-up in the cardiology clinic in 3 years is scheduled.   **HP**

REFERENCES

1. Rosenthal A. How to distinguish between innocent and pathologic murmurs in childhood. Pediatr Clin North Am 1984;31:1229–40.
2. Young PC. The morbidity of cardiac nondisease revisited. Is there lingering concern associated with an innocent murmur? Am J Dis Child 1993;147:975–7.
3. Gutgesell HP, Barst RJ, Humes RA, et al. Common cardiovascular problems in the young. Part I. Murmurs, chest pain, syncope and irregular heart rhythms. Am Fam Physician 1997;56:1825–30.
4. Newburger JW, Rosenthal A, Williams RG, et al. Noninvasive tests in the initial evaluation of heart murmurs in children. N Engl J Med 1983;308:61–4.
5. McCrindle BW, Shaffer KM, Kan JS, et al. Factors prompting referral for cardiology evaluation of heart murmurs in children [letter]. Arch Pediatr Adolesc Med 1995;149:1277–9.
6. Danford DA, Nasir A, Gumbiner C. Cost assessment of the evaluation of heart murmurs in children. Pediatrics 1993;91:365–8.
7. Hurwitz RA, Caldwell RL. Should pediatric echocardiography be performed in adult laboratories [abstract]? Pediatrics 1998;102:E15.
8. McCrindle BW, Shaffer KM, Kan JS, et al. Cardinal clinical signs in the differentiation of heart murmurs in children. Arch Pediatr Adolesc Med 1996;150:169–74.
9. DeGroff CG, Bhatikar S, Hertzberg J, et al. Artificial neural network-based method of screening heart murmurs in children. Circulation 2001;103:2711–6.
10. MacLaren MJ, Lachman AS, Pocock WA, Barlow JB. Innocent murmurs and third heart sounds in black school children. Br Heart J 1980;43:67–73.
11. Richards MR, Merritt KK, Samuels MH, Langmann AG.

Frequency and significance of cardiac murmurs in the first year of life. Pediatrics 1955;15:169–79.

12. Still GF. Common disorders and diseases of childhood. London: Frowde; 1915.

13. Stein PD, Sabbah HN. The aortic origin of innocent murmurs. Am J Cardiol 1977;39:665–71.

14. Gardiner HM, Joffe HS. Genesis of Still's murmurs: a controlled Doppler echocardiographic study. Br Heart J 1991;66:217–20.

15. Harris TN, Saltzman HA, Needleman HL, Lisker L. Spectrographic comparison of ranges of vibration frequency among innocent cardiac murmurs in childhood and some murmurs of valvular insufficiency. Pediatrics 1957;19:57–67.

16. Castle RL. Clinical recognition of innocent cardiac murmurs in children. JAMA 1961;177:71–5.

17. Leatham A, Segal BL, Shafter H. Auscultatory and phonocardiographic findings in healthy children with systolic murmurs. Br Heart J 1963;25:451–9.

18. Miyake T, Yokoyama T. Evaluation of transient heart murmur resembling pulmonary artery stenosis in term infants by Doppler and M-mode echocardiography. Jpn Circ J 1993;57:77–83.

19. Nelson WP, Hall RJ. The innocent supraclavicular arterial bruit: utility of shoulder maneuvers in its recognition. N Engl J Med 1968;278:778.

20. Jones Fl Jr. Frequency, characteristics, and importance of the cervical venous hum in adults. N Engl J Med 1962;267:658–60.

21. Hurst JW, Staton J, Hubbard D. Precordial murmur during pregnancy and lactation. N Engl J Med 1958;259:515–7.

22. White PD, Adams FD, Craib D. A note on cardiac murmurs. Recommendation for a revised terminology. Am J Med Sci 1942;203:52–4.

23. Samanek M, Slavik Z, Zborilova B, et al. Prevalence, treatment, and outcome of heart disease in live-born children: a prospective analysis of 91,823 live-born children. Pediatr Cardiol 1989;10:205–11.

24. Whittemore R, Wells JA, Castellsague X. A second-generation study of 427 probands with congenital heart defects and their 837 children. J Am Coll Cardiol 1994;23:1459–67.

25. Torfs CP, Christianson RE. Anomalies in Down syndrome individuals in a large population-based registry. Am J Med Genet 1998;77:431–8.

26. Garne E, Nielsen G, Hansen OK, Emmertsen K. Tetralogy of Fallot. A population-based study of epidemiology, associated malformations and survival in western Denmark 1984–1992. Scand Cardiovasc J 1999;33:45–8.

27. Copel JA, Pilu G, Kleinman CS. Congenital heart disease and extracardiac anomalies: associations and indications for fetal echocardiography. Am J Obstet Gynecol 1986:154:1121–32.

28. Wallgren EI, Landtman B, Rapola J. Extracardiac malformations associated with congenital heart disease. Eur J Cardiol 1978;7:15–24.

29. Hwa J, Richards JG, Huang H, et al. The natural history of aortic dilatation in Marfan syndrome. Med J Aust 1993;158:558–62.

30. Pyeritz RE, Wapple MA. Mitral valve dysfunction in the Marfan syndrome. Clinical and echocardiographic study of prevalence and natural history. Am J Med 1983;74:797–807.

31. Towbin JA. Molecular genetic aspects of cardiomyopathy. Biochem Med Metabol Biol 1993;49:285–320.

32. Chatelain P, Oberhansli I, Friedli B. Physiological pulmonary branch stenosis in newborns: 2D-echocardiographic and Doppler characteristics and follow up. Eur J Pediatr 1993;152:559–63.

33. Klewer SE, Donnerstein RL, Goldberg SJ. Still's-like innocent murmur can be produced by increasing aortic velocity to a threshold value. Am J Cardiol 1991;68:810–2.

34. Mehrizi A, Drash A. Growth disturbance in congenital heart disease. J Pediatr 1962;61:418–29.

35. Haring OM, Luisada AA, Gasul BM. Phonocardiography in patent ductus arteriosus. Circulation 1954;10:501–10.

36. Leatham A, Segal B. Auscultatory and phonocardiographic signs of ventricular septal defect with left-to-right shunt. Circulation 1962;25:318–27.

37. Rahko PS. Prevalence of regurgitant murmurs in patients with valvular regurgitation detected by Doppler echocardiography. Ann Intern Med 1989;111:466–72.

38. Leatham A, Gray IR. Auscultatory and phonocardiographic signs of atrial septal defect. Br Heart J 1956;18:193–208.

39. Vogelpoel L, Schrire V. Auscultatory and phonocardiographic assessment of pulmonary stenosis and intact ventricular septum. Circulation 1960;22:55–72.

40. Perloff JK. Clinical recognition of aortic stenosis. The physical signs and differential diagnosis of the various forms of obstruction to left ventricular outflow. Prog Cardiovasc Dis 1968;10:323–52.

41. Danford DA, Martin AB, Fletcher SE, et al. Children with heart murmurs: can ventricular septal defect be diagnosed reliably without an echocardiogram? J Am Coll Cardiol 1997;30:243–6.

42. Danford DA, Salaymeh KJ, Martin AB, et al. Pulmonary stenosis: defect-specific diagnostic accuracy of heart murmurs in children. J Pediatr 1999;134:76–81.

43. Danford DA, Fletcher SE, Martin AB, Gumbiner CH. Accuracy of clinical diagnosis of left heart valvular or obstructive lesions in pediatric outpatients with heart murmur. Am J Cardiol 2002;89:878–84.

44. Danford DA. Role of echocardiography in the initial assessment of heart murmurs. Pediatr Ultrasound Today 1999;4:57–80.

45. Ritter DG, Feldt RH, Weidman WH, DuShane JW. Five congenital cardiac defects: study of the profile and natural history. Ventricular septal defect. Circulation 1965;31 (Suppl III):III 42–52.

46. Weidman WH, Blount SG Jr, DuShane JW, et al. Clinical course in ventricular septal defect. Circulation 1977;56

(1 Suppl):I56–69.

47. Levine OR, Blumenthal S. Five congenital cardiac defects: study of their profile and natural history. Pulmonic stenosis. Circulation 1965;31(Suppl III):III33–41.

48. Zaver AG, Nadas AS. Five congenital cardiac defects: study of the profile and natural history. Atrial septal defect-secundum type. Circulation 1965;32(Suppl III):III24–32.

49. Hohn AR, Van Praagh S, Moore AAD, et al. Five congenital cardiac defects: study of the profile and natural history. Aortic stenosis. Circulation 1965;31(Suppl III):4–12.

50. Fogel MA, Lieb DR, Seliem MA. Validity of electrocardiographic criteria for left ventricular hypertrophy in children with pressure- or volume-loaded ventricles: comparison with echocardiographic left ventricular muscle mass. Pediatr Cardiol 1995;16:261–9.

51. Swenson JM, Fischer DR, Miller SA, et al. Are chest radiographs and electrocardiograms still valuable in evaluating new pediatric patients with heart murmurs or chest pain? Pediatrics 1997;99:1–3.

52. Birkebaek NH, Hansen LK, Oxhoj H. Diagnostic value of chest radiography and electrocardiography in the evaluation of asymptomatic children with a cardiac murmur. Acta Paediatr 1995;84:1379–81.

53. Steinberg I. Roentgenography of patent ductus arteriosus. Am J Cardiol 1964;13:698–707.

54. Marek J, Skovranek J, Hucin B, et al. Seven-year experience of noninvasive preoperative diagnostics in children with congenital heart defects: comprehensive analysis of 2,788 consecutive patients. Cardiology 1995;86:488–95.

55. Stanger P, Silverman NH, Foster E. Diagnostic accuracy of pediatric echocardiograms performed in adult laboratories. Am J Cardiol 1999;83:908–14.

56. Danford DA, Martin AB, Fletcher SE, Gumbiner CH. Echocardiographic yield in children when innocent murmur seems likely but doubts linger. Pediatr Cardiol 2002;23:410–4.

57. Yi MS, Kimball TR, Tsevat J, et al. Evaluation of heart murmurs in children: cost-effectiveness and practical implications. J Pediatr 2002;141:504–11.

58. Rajakumar K, Weisse M, Rosas A, et al. Comparative study of clinical evaluation of heart murmurs by general pediatricians and pediatric cardiologists. Clin Pediatr (Phila) 1999;38:511–8.

59. Van Oort A, LeBlanc-Botden M, De Boo T, et al. The vibratory innocent murmur in schoolchildren: difference in auscultatory findings between school medical officers and a pediatric cardiologist. Pediatr Cardiol 1994;15:282–7.

60. Smythe JF, Teixeira OH, Vlad P, et al. Initial evaluation of heart murmurs: are laboratory tests necessary? Pediatrics 1990;86:497–500.

61. Geva T, Hegesh J, Frand M. Reappraisal of the approach to the child with heart murmurs: is echocardiography mandatory? Int J Cardiol 1988;19:107–13.

62. Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. Circulation 1968;37:805–15.

63. Fisher RG, Moodie DS, Sterba R, Gill CC. Patent ductus arteriosus in adults—long-term follow-up: nonsurgical versus surgical treatment. J Am Coll Cardiol 1986;8:280–4.

64. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Br Med J 1958;2:701–9.

65. Gersony WM, Hayes CJ, Driscoll DJ, et al. Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. Circulation 1993;87(2 Suppl):I121–6.

66. Corone P, Doyon F, Gaudeau S, et al. Natural history of ventricular septal defect. A study involving 790 cases. Circulation 1977;55:908–15.

67. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1997;277:1794–801.

68. Kimball TR, Daniels SR, Meyer RA, et al. Effect of digoxin on contractility and symptoms in infants with large ventricular septal defect. Am J Cardiol 1991;68:1377–82.

69. Sluysmans T, Styns-Cailteux M, Tremouroux-Wattiez M, et al. Intravenous enalaprilat and oral enalapril in congestive heart failure secondary to ventricular septal defect in infancy. Am J Cardiol 1992;70:959–62.

70. Moller JH, Patton C, Varco RL, Lillehei CW. Last results (30 to 35 years) after operative closure of isolated ventricular septal defect from 1954 to 1960. Am J Cardiol 1991;68:1491–7.

71. Actis Dato GM, Cavaglia M, Aidala E, et al. [Patent ductus arteriosus. Follow-up of 677 operated cases 40 years later.] [Article in English, Italian.] Minerva Cardioangiol 1999;47:245–54.

72. Patel HT, Cao QL, Rhodes J, Hijazi ZM. Long-term outcome of transcatheter coil closure of small to large patent ductus arteriosus. Catheter Cardiovasc Interv 1999;47:457–61.

73. Campbell M. Natural history of atrial septal defect. Br Heart J 1970;32:820–6.

74. Campbell M. Natural history of persistent ductus arteriosus. Br Heart J 1968;30:4–13.

75. Driscoll D, Allen HD, Atkins DL, et al. Guidelines for evaluation and management of common congenital cardiac problems in infants, children, and adolescents. A statement for healthcare professionals from the Committee on Congenital Cardiac Defects of the Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 1994;90:2180–8.

76. Keane JF, Driscoll DJ, Gersony WM, et al. Second natural history study of congenital heart defects. Results of treatment of patients with aortic valvar stenosis. Circulation 1993;87(2 Suppl):I16–27.

77. Cohen M, Pocock WA, Lakier JB, et al. Four-year follow-up of black school children with nonejection clicks and mitral systolic murmurs. Am Heart J 1978;95:697–701.

78. Devereux RB, Kramer-Fox R, Shear MK, et al. Diagnosis and classification of severity of mitral valve prolapse: methodologic, biologic, and prognostic considerations.

Am Heart J 1989;113:1265–80.

79. Brouwer RM, Erasmus ME, Ebels T, Eijgelaar A. Influence of age on survival, late hypertension, and recoarctation in elective aortic coarctation repair. Including long-term results after elective aortic coarctation repair with a follow-up from 25 to 44 years. J Thorac Cardiovasc Surg 1994;108:525–31.

80. Fletcher SE, Nihill MR, Grifka RG, et al. Balloon angioplasty of native coarctation of the aorta: midterm follow-up and prognostic factors. J Am Coll Cardiol 1995;25: 730–4.

81. Jarrar M, Betbout F, Farhat MB, et al. Long-term invasive and noninvasive results of percutaneous balloon pulmonary valvuloplasty in children, adolescents, and adults. Am Heart J 1999; 138(5 Pt 1):950–4.

82. Wang JK, Lue HC, Wu MH, Young ML. Efficacy of balloon valvuloplasty in treating mild pulmonary stenosis. Acta Cardiol 1992;47:349–55.

83. Mendelsohn AM, Banerjee A, Meyer RA, Schwartz DC. Predictors of successful pulmonary balloon valvuloplasty: 10-year experience. Cathet Cardiovasc Diagn 1996;39: 236–43.

84. Wagner HR, Ellison RC, Keane JF, et al. Clinical course in aortic stenosis. Circulation 1977;56(1 Suppl);I47–56.

85. Justo RN, McCrindle BW, Benson LN, et al. Aortic valve regurgitation after surgical versus percutaneous balloon valvotomy for congenital aortic valve stenosis. Am J Cardiol 1996;77:1332–8.

86. Stein PD, Alpert JS, Copeland J, et al. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 1992;102 (4 Suppl):445S–455S.

87. Knott-Craig CJ, Elkins RC, Santangelo KL, et al. Aortic valve replacement: comparison of late survival between autografts and homografts. Ann Thorac Surg 2000;69: 1327–32.

88. Elkins RC, Knott-Craig CJ, Ward KE, Lane MM. The Ross operation in children: 10-year experience. Ann Thorac Surg 1998;65:496–502.

89. Giuffre RM, Walker I, Vaillancourt S, Gupta S. Opening Pandora's box: parental anxiety and the assessment of childhood murmurs. Can J Cardiol 2002;18:406–14.

90. Geggel RL, Horowitz LM, Brown EA, et al. Parental anxiety associated with referral of a child to a pediatric cardiologist for evaluation of a Still's murmur. J Pediatr 2002;140:747–52.

91. Bergman AB, Stamm SJ. The morbidity of cardiac nondisease in schoolchildren. N Engl J Med 1967;276:1008–13.

92. McCrindle BW, Shaffer KM, Kan JS, et al. An evaluation of parental concerns and misperceptions about heart murmurs. Clin Pediatr (Phila) 1995;34:25–31.

93. Friedman S. Some thoughts about functional or innocent murmurs. Clin Pediatr (Phila) 1973;12:678–9.

The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. Microalbuminuria Study Group. N Engl J Med 2001;345:870–8.

82. Hilgers KF, Mann JF. ACE inhibitors versus AT(1) receptor antagonists in patients with chronic renal disease. J Am Soc Nephrol 2002;13:1100–8.

83. Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microaluminuria (CALM) study. BMJ 2000;321:1440–4.

84. Agarwal R. Add-on angiotensin receptor blockade with maximized ACE inhibition. Kidney Int 2001;59:2282–9.

85. Chrysostomou A, Becker G. Spironolactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease [letter]. N Engl J Med 2001;345: 925–6.