Review

Missed or Delayed Diagnosis of Heart Disease by the General Pediatrician

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Posted Date: 17 March 2024

doi: 10.20944/preprints202403.0867.v1

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Missed or Delayed Diagnosis of Heart Disease by the General Pediatrician

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Abstract: Primary care pediatricians encounter a wide range of complex conditions in their daily clinical practice. It is not uncommon for their patients to get exposed to medical errors. Diagnostic errors, defined as missed, delayed, or wrong diagnosis, are of great importance as they may cause significant harm to the pediatric patient with severe disease. These errors often occur when the symptoms and signs of a disease are atypical or missing. Data on the most frequent misdiagnosed situations in pediatrics is scarce. One of these groups of conditions is that regarding cardiac diseases. The pediatric cardiology field has met rapid development over the past few decades. Primary care providers play a key role in diagnosis, management, and referral of children with heart disease, both congenital and acquired, because many common cardiac complaints are first addressed in the primary care setting. The scope of this review is to investigate the cardiac entities that are often missed by the general pediatricians. In particular, it aims to spot the most common of them, to describe their clinical presentation, their diagnostic options, red flags, and tips, and to provide the ways to avoid erroneous, delayed, or missed diagnosis.

Keywords: congenital heart disease; acquired heart disease; children; diagnostic errors; missed diagnosis; delayed diagnosis; primary care pediatrician

1. Introduction

Congenital heart disease (CHD) is the most frequent congenital disorder in the newborns and the most frequent cause of death from birth defects in infancy [1,2]. Congenital heart defects occur in approximately 1% of live births and range from benign to life threatening [3]. They become manifest at different ages, with clinical signs and symptoms ranging from the incidental identification of a heart murmur to cyanosis, congestive heart failure, or cardiovascular collapse, or depending on the anatomy and physiology of the lesion [4]. The incidence of severe CHD that will require expert pediatric cardiology management in infancy is 2.5 to 3 per 1,000 live births. The moderately severe forms of CHD probably account for another 3 per 1,000 live births, although another 13 per 1,000 live births have bicuspid aortic valves that will also need cardiologic care in adulthood [3]. Long-term survivors of CHD are at risk for a number of postoperative complications and require life-long specialized medical care [5,6].

Acquired heart disease is much more common in adults than in children. The two most common acquired conditions among children are rheumatic heart disease and Kawasaki disease. Multiple studies have confirmed rheumatic fever as the leading cause of acquired heart disease in children in developing countries [7]. On the contrary, Kawasaki disease is the most prevalent acquired pediatric heart disease in the developed world [8]. Acquired heart disease in pediatrics also includes myocarditis, pericarditis, endocarditis, and cardiomyopathies. Cardiomyopathy refers to a

 doi:10.20944/preprints202403.0867.v1

heterogeneous group of disorders involving abnormalities of the myocardial muscle. They may be inherited or acquired and are usually classified into distinct groups: dilated, hypertrophic, non-compaction of the ventricular myocardium, arrhythmogenic dysplasia of the right ventricle and restrictive cardiomyopathy [9].

Over time, increasing attention is paid to those diseases since they significantly impact the quality of life of young patients. The burden of acquired heart disease in children is significant and may be equivalent to that of congenital heart disease [10]. Great progress has been recently made in the diagnosis and management of these diseases in children [8,11]. Moreover, the treatment and the outcomes may be different for children compared to adults with the same disease, because of the unique physiology of childhood which involves normal growth and development [8,9,11].

Primary care practitioners encounter a wide range of complex conditions in their daily clinical practice. It is not uncommon for their patients to get exposed to medical errors [12–17]. Errors happen when the correct diagnosis is unintentionally delayed, although sufficient information was available, but was not appreciated by the physician. Other forms of medical errors are the situations when a wrong diagnosis is initially made before the correct one is established, or when a definitive diagnosis is never made and thus the condition of the patient remains undiagnosed [17]. Diagnostic errors of severe diseases may cause significant harm to the patient [12–16]. Diagnostic errors often occur when the symptoms and signs of a disease are atypical or missing [12,16]. Data concerning diagnostic errors in pediatric clinical practice is especially limited [16,19].

As far as the field of paediatric cardiology is concerned, the diagnosis of heart disease is also often delayed or missed by the office pediatricians who are in the front line for the care of children, and their responsibility includes among others clearance for sports activities, and reassurance of parents for their child's normality [18–20]. Critical heart disease has signs and symptoms which are subtle or mimic other common benign illnesses of childhood and is often underdiagnosed [18–20]. Missed or delayed diagnosis causes significant morbidity and mortality due to cardiovascular compromise and organ dysfunction, including central nervous system hypoxia before treatment initiation [21,22].

The primary aim of this review is to describe the most common cardiac conditions that are often missed by the primary care pediatrician. The secondary aim is to provide the reader with information to be able to:

1. Identify red flags associated with severe pediatric cardiac conditions that may mimic benign pathologic conditions.
2. Understand which critical cardiac conditions may be missed with pulse oximetry screening of the newborn and how they will later present.
3. Get familiar with the four questions that are currently recommended by the American Academy of Pediatrics to be asked by the primary care pediatrician to all children, to screen for cardiac conditions which are associated with increased risk of sudden cardiac death.

2. Pediatric Heart Failure

Heart failure in the pediatric patient remains a devastating diagnosis for children and their families and represents a diagnostic and therapeutic dilemma for medical providers [23]. Due to its rarity, most practitioners in the primary care or emergency departments have little practical experience with its presentation or management in children [24]. Furthermore, significant overlap often occurs in symptoms and physical examination findings with more common pediatric conditions, and timely diagnosis of heart failure in children is dependent on a high index of suspicion and thoughtful use of diagnostic studies [23,24]. Timely recognition and appropriate treatment are particularly difficult in pediatric heart failure, given its marked heterogeneity in the underlying causes, pathophysiology, and clinical presentation [25].

Presenting features of heart failure such as tachypnea, feeding difficulties, abdominal pain, and nausea may be incorrectly attributed to respiratory infections or gastroenteritis [23,25]. Prompt diagnosis and management is essential to reduce significant morbidity and mortality [24,25].

 doi:10.20944/preprints202403.0867.v1

Misdiagnosis is common, especially in early stages [18,23]. Nearly one-half of children with unknown heart disease who are hospitalized with systolic heart failure are missed at first presentation and undergo significant irrelevant treatment and investigations. Initial presentation to the primary care physician, longer duration of symptoms before presentation, and nausea/emesis have been associated with missed diagnosis [18].

Heart failure is a syndrome in which a patient demonstrates clinical symptoms due to an imbalance between cardiac output and metabolic demands, usually due to a functional or anatomical abnormality of the heart. In other words, it is the failure of the heart to supply adequate blood to systemic or pulmonary circulation or to receive venous return at an appropriate filling pressure, resulting in deficiency of the circulation and adverse effects to the patient [24]. Although common in adults, heart failure is relatively uncommon in children [26]. In the United States, 11,000– 14,000 children are annually admitted with heart failure [27].

In the developed world, congenital heart disease and cardiomyopathies are two leading causes of heart failure in the pediatric population, with other major causes including rhythm and conduction disturbances and acquired heart diseases [26]. In children with a structurally normal heart, myocarditis and primary cardiomyopathies are the most commonly acquired etiologies. Myocarditis and dilated cardiomyopathy may mimic other respiratory or viral illnesses, but hepatomegaly or the finding of cardiomegaly and an abnormal electrocardiogram may help distinguish these entities from other more common pediatric illnesses [28,29].

Clinical presentation of heart failure in children can be quite variable and nonspecific. It can be differently expressed, based on the chronicity of the disease and the age of the patient [18]. In addition, there is considerable overlap between symptoms of heart failure and more common pediatric conditions like asthma, pneumonia, and gastroenteritis. Initial signs and symptoms can be diagnosed as respiratory, gastroenterological, and cardiac [18]. Respiratory symptoms including cough, shortness of breath, increased work of breathing and tachypnea are seen in 68–80% of patients [28–30]. Respiratory examination may identify crackles, rales, and wheezing, while hypoxemia may be present as well.

Gastroenterological symptoms including abdominal pain, nausea, vomiting, decreased appetite, weight loss and feeding intolerance are also common, with up to 89% of children reporting at least one symptom related to the digestive system. Thus, heart failure should be included in the differential diagnosis of children presenting with gastrointestinal symptoms [31]. Although often seen together with respiratory or cardiac symptoms, *children presenting to the emergency department in heart failure may have only gastroenterological complaints.* Gastroenterological symptoms are more common in adolescents, whereas respiratory complaints are more prevalent in younger children [31]. Poor feeding and failure to thrive are common clinical presentations of heart failure in infants [24]. When present, hepatomegaly can be a helpful examination finding as it is uncommon in children and more specific to heart failure, though its absence does not exclude heart failure diagnosis, as only 36–65% of children with heart failure present with this finding [28–30]. Chest pain has been reported in 24–45% of patients but it is rare in younger children. Tachycardia is relatively common, seen in 32–58% of patients, though its diagnostic utility is limited by lack of specificity [28–30].

Suspicion for heart failure should prompt urgent consultation with a pediatric cardiologist and early consideration of transfer to a specialized pediatric cardiology center. Increased awareness among pediatricians, and policymakers regarding missed or delayed diagnosis as well as timely and effective management and supportive care of children with heart failure is critical to meet the needs of this complex patient population and improve outcome [23].

3. Pediatric Myocarditis

Myocarditis is a rare inflammation of the muscular walls of the heart and remains a diagnostic challenge in the pediatric clinical setting because of the variability of presentation [24,29,32–34]. Patients of all ages may be affected, but most cases occur in infants and teenagers. More than half of all cases are seen in the first year of life [33]. Its impact on lifelong morbidity and mortality is significant [32,33,35]. It accounts for nearly one half of all cases of dilated cardiomyopathy in children

 doi:10.20944/preprints202403.0867.v1

[32,33]. The course of patients with myocarditis is heterogeneous, varying from partial or full clinical recovery in a few days, to advanced low cardiac output syndrome requiring mechanical circulatory support or heart transplantation [33,34]. Myocarditis is also identified as a cause of sudden unexpected death in young patients [33,34,36,37].

Myocarditis in children is most often caused by a viral or infectious etiology, with two new etiologies related to COVID-19 infection and the COVID-19 mRNA vaccine, of which long-term sequelae are unknown [34]. Vaccine-associated myocarditis has been reported more commonly in adolescent and adult males and recovery has been complete in most cases [34]. Children are at greater risk of developing myocarditis secondary to COVID-19 compared to the mRNA COVID-19 vaccine [34]. Specific viral causes have been identified by polymerase chain reaction analysis of myocardial biopsy tissue. It has been demonstrated that the prevalence of specific viruses has shifted over time from adenovirus and enteroviruses to parvovirus B19 and human herpesvirus 6 [38]. Despite this shift, a wide spectrum of infectious and noninfectious etiologies of myocarditis remains [34].

Myocarditis is an important diagnosis, as it is the most common etiology of heart failure in previously healthy pediatric patients [37]. Unless a high index of suspicion is maintained, acute myocarditis may easily be missed, and the diagnosis may become obvious when fulminant disease is present [29,32,33]. Given its variable clinical presentation, the diagnosis is frequently missed, making it difficult to quantify the true incidence and prevalence of the disease [29,32–34]. Children with myocarditis are presented with symptoms that can be mistaken for other types of illnesses, with non-specific symptoms which are often missed by clinicians [29,32,34]. There are no pathognomonic clinical features. Symptoms of acute myocarditis vary, often starting with flu-like symptoms, either of the upper respiratory or gastrointestinal tract before any cardiac symptoms appear [29,34]. The presentation is acute or insidious in onset and progression. Even patients with mild symptoms are at risk of deterioration, and therefore early diagnosis is important in establishing appropriate monitoring and supportive care [33,35].

The diagnosis is made based on clinical presentation and echocardiographic findings and requires a high degree of clinical suspicion [33–35]. While the gold standard for diagnosing myocarditis was previously endomyocardial biopsy, with the new revised Lake Louise Criteria, cardiovascular magnetic resonance has emerged as an important non-invasive imaging tool to assist in diagnosis [3,29,33,35,39]. Cardiovascular magnetic resonance allows for assessment of ventricular function and tissue characterization, with newer techniques, such as myocardial strain, to help guide management both acutely and long term [34].

Patients often present with prodromal symptoms that are initially not recognized to be associated with myocarditis [29,32,34]. Clinical characteristics at presentation may involve malaise, fatigue, anorexia, shortness of breath, fever, rhinorrhea, mild chest pain, orthopnea, presyncope, dyspnea, cough, palpitations, mild abdominal pain, and diarrhea [29,34]. History of a preceding viral prodrome is present in about two-thirds of patients [29,34]. Severe clinical signs may include tachypnea, tachycardia, hepatomegaly, respiratory distress, new onset murmur, gallop, diminished pulses, edema, and cyanosis [34,35].

Acute severe myocarditis presents with heart failure and cardiovascular collapse [32,34]. Fever has been reported in > 50% of patients [36]. Arrhythmias occur in up to 45% and include ventricular and atrial arrhythmias and high-grade atrioventricular block [40,41]. Syncope occurs in about 10% [42]. Myocarditis can also present with sudden cardiac death and has been identified in 6% of young athletes with sudden cardiac death in the United States [36,42].

Because of the potential for severe and fatal disease, it is important to identify myocarditis and dilated cardiomyopathy early, so that monitoring and supportive treatment can be timely established [34,35]. In case reviews of children admitted with myocarditis, 84% of had multiple visits to medical providers before being correctly diagnosed [33,34]. Most patients were initially misdiagnosed as having either sepsis or pneumonia/asthma [32,35]. Alternatively, children may present with nausea and vomiting and may be mistakenly diagnosed as having gastroenteritis [32].

 doi:10.20944/preprints202403.0867.v1

4. Pediatric Pulmonary Arterial Hypertension

Pediatric pulmonary arterial hypertension (PAH) is a rare entity characterized by increased pressure in the pulmonary arteries, caused by an heterogeneous group of diseases with different underlying causes in different age groups and with substantial morbidity and mortality [43–47]. As with any rare disease, the low prevalence in the general pediatric population increases the risk of missed diagnosis. Pulmonary hypertension can occur at any age during childhood and like in adults a delay in diagnosis is common [43–47]. Historical outcomes for idiopathic pediatric pulmonary arterial hypertension are worse compared to adults [45]. In the era before targeted therapy, the median survival from diagnosis of idiopathic pulmonary arterial hypertension in children was 10 months [45]. Without treatment, increase of pulmonary arterial pressure and resistance in patients with PAH leads to right heart failure and death. PAH in children is linked to lung growth and because of this advantage, the child with PAH has greater potential to reverse the underlying pathologic condition with appropriate therapy [48].

Delays in making the diagnosis 1 to 2 years after the onset of the disease are not uncommon in pediatric PAH, which is attributed to the nonspecific nature of early symptoms [47]. In the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP registry), the most common presenting symptoms were dyspnea on exertion, fatigue, and syncope [46,49]. Children with PAH are often misdiagnosed, with more common childhood conditions such as asthma, vasovagal syncope, or seizures before being diagnosed with PAH [47]. Symptoms are less specific in infants, and may involve poor appetite, failure to thrive, diaphoresis, tachypnea, tachycardia, and irritability. Syncope, presyncope, and chest pain are features of more advanced diseases, with hemoptysis being a late and sometimes fatal symptom [50]. A standardized approach to diagnostic testing has been recommended in the recently published American Heart Association and American Thoracic Society Joint Guidelines for Pediatric PAH Guidelines [51].

The definition of pulmonary hypertension has changed recently, based in part on contemporary outcome data and focusing on early disease detection. Now, PAH includes patients with mean pulmonary artery pressure > 20 mm Hg, measured by right heart catheterization. These lowered thresholds aim to identify patients early in the disease course, which is important because delay to diagnose PAH is associated to increased morbidity and shortened lifespan [52]. Determination of pulmonary artery pressure by Doppler echocardiography is central to patient screening and evaluation. The velocity of the tricuspid regurgitation jet, when adequate, should be recorded to assess right ventricular systolic pressure, which in the absence of right ventricular outflow obstruction reflects systolic pulmonary artery pressure [53]. Catheterization should generally be performed at diagnosis before the initiation of pulmonary hypertension-targeted therapy [46,51].

As a result of disease rarity and complexity and the importance of clinical experience with specific diagnostic procedures and therapeutic strategies, the evaluation and care of pediatric pulmonary hypertension patients should be provided by specialized pulmonary hypertension centers that include multidisciplinary medical subspecialists, with special expertise. Upon suspicion, it is important to perform a thorough evaluation for secondary causes of PAH and following expert opinion confirm diagnosis with cardiac catheterization [54].

The outcome for children with PAH has improved significantly when targeted treatment options became available, however it depends on the condition of the individual patient and the cause and severity of PAH [50,55]. This is attributed to the increased awareness of the disease and its multiple etiologies, more accurate diagnosis, better risk stratification, and early initiation of combination pharmacotherapy. However, despite the availability of new drug therapies, long-term outcomes for children with severe PAH remains poor [55].

5. Coarctation of the Aorta

Coarctation of aorta (CoA) is often a discrete narrowing of the aorta, but it can be long segment and/or tortuous, causing obstruction to the flow of blood to the systemic circulation [56]. It accounts for 6–8% of all congenital heart diseases and has an incidence of 2.5 to 4 per 10,000 live births [3,57].

 doi:10.20944/preprints202403.0867.v1

The most common location of CoA is just distally to the origin of the left subclavian artery at the point where the arterial duct connects to the aorta.

Most cases fall into one the following categories: critical coarctation that becomes manifest in the neonatal period when the arterial duct closes and which if left untreated is lethal, and asymptomatic CoA that presents later in childhood, usually with arterial hypertension in the upper limbs [58]. Critical CoA represents about 60% of all cases. The most commonly associated anomaly is a bicuspid aortic valve with a prevalence up to 45–62% in these patients [59,60].

Critical CoA in neonates is a common cause of shock and death. It may be *the most difficult of all forms of critical congenital heart disease to diagnose* because the obstruction does not appear until several days after birth, after discharge from the hospital and because there are no characteristic murmurs [61–63]. At birth, the ductus is wide open so that blood can flow freely from the ascending to the descending aorta and the neonate is asymptomatic. Infants with CoA are discharged from the nursery without symptoms or signs of heart disease, not only because the arterial duct is open and provides the blood supply to the lower body, but also because the way that it closes delays the development of obstruction [61–63]. Ductal closure begins in the middle and progresses towards the edges, which may leave the aortic side which is opposed to the site of coarctation relatively large for some time. These infants even with severe CoA become symptomatic usually at 7 to 14 days [64]. Infants who have ductal tissue surrounding the area of coarctation develop obstruction as the arterial duct begins to constrict resulting to a very early clinical deterioration [58]. Decreased femoral pulses and upper limb hypertension usually are present before this time, underlying the importance of regular checking of brachial and femoral pulses by the primary care pediatrician to timely identify CoA at birth and through the first month of life, thus preventing the clinical deterioration and cardiovascular collapse of the infant [65].

When pulse oximetry screening for critical congenital heart disease in neonates was introduced, there was a strong belief that pulse oximetry might solve the problem of timely diagnosis of CoA, thus preventing neonates from presenting with cardiovascular collapse or even dying suddenly in the second or third week of life, when the arterial duct which was associated with right-to-left flow closes [66]. Unfortunately, this occurs in a minority of neonates and therefore pulse oximetry cannot be relied upon for the diagnosis of critical CoA [66].

Although the diagnosis of CoA in older children is straightforward, the diagnosis is often missed or delayed [67,68]. In older patients the clinical diagnosis is based on finding hypertension in the arms, weak and delayed femoral arterial pulses, and upper body collateral circulation. Collateral arteries are identified in over 50% of older patients and are associated with a systolic or continuous murmur radiating to scapula or over the thorax [56]. Collateral Circulation in native CoA develops predominantly from intercostal and subclavian arterial branches as a function of age and severity of CoA. They are more likely heard than felt in the interscapular area, though palpable collateral arteries may be more reliable. Native CoA with good collateral circulation may present without hypertension, and collateral circulation may mask the diagnostic discrepancy between the upper and lower limb pulses. Palpable axillary collateral circulation can be diagnostic in such instances [69].

Blood pressure should be taken with an appropriate-sized cuff in both arms because the left subclavian artery is often hypoplastic or distal to the coarctation. The right subclavian artery is aberrant in more than 1% of population and could originate peripherally to the coarctation site [65]. If the arm pressure is high and is associated with weak and delayed femoral pulses in comparison to the brachial, the next step is obtaining a leg blood pressure with an appropriate-sized cuff.

In older children, CoA is missed in about 85% of patients referred to hospital for murmurs or hypertension [65,67,68]. In a study published in 1982, significant delays in diagnosis occurred in the great majority of patients. The median age at diagnosis was 10 years. However, the diagnosis of coarctation of the aorta was made before referral in only 14% of these cases. The remaining referrals were made after the incidental notation of hypertension or a heart murmur [67]. In a repeat study performed at the same institution 14 years later, the mean age of diagnosis of coarctation was 8.4 years. A specific diagnosis was made in 4% before referral to a pediatric cardiologist. CoA would have been missed in 82% of children if absent lower-extremity pulses were required as a diagnostic

 doi:10.20944/preprints202403.0867.v1

feature [68]. These findings were similar to those reported in the previous decade, suggesting that early detection of CoA has not improved with time.

6. Kawasaki Disease

Kawasaki disease (KD) is an unknown etiology self-limited acute vasculitis of the medium caliber muscular arteries, which represents the most common cause of acquired heart disease in children in the developed world and predominantly affects children under five years of age [8,70]. Complications of KD include cardiovascular (vasculitis, endocarditis, myocarditis, pericarditis), gastrointestinal (sialoductitis, enteritis, hepatitis, cholangitis, pancreatitis and pancreatic ductitis), respiratory (bronchitis, segmental interstitial pneumonia), genitourinary (cystitis, focal interstitial nephritis, prostatitis), nervous system involvement (aseptic leptomeningitis, choriomeningitis, ganglionitis, neuritis) and hematopoietic abnormalities (lymphadenitis, splenitis, thymitis) [71].

The most important complications are coronary artery aneurysms which are seen in up to 25 % of untreated cases [8,70]. KD arteriopathy is characterized by three pathologic processes: necrotizing arteritis, subacute/chronic arteritis, and luminal myofibroblastic proliferation [71]. Necrotizing arteritis occurs in the first two weeks after the onset of the disease and can result in coronary artery aneurysm formation, which if giant is associated with severe adverse cardiovascular outcome [8,70,71]. Subacute/chronic arteritis begins in the first two weeks and can continue for months to years after the onset of the disease [71]. Prompt therapy is required, because delayed or unrecognized KD can lead to lifelong heart disease or death in previously healthy children [71]. Early treatment within 10 days of illness with intravenous immunoglobulin (IVIG) decreases the incidence of coronary artery aneurysms from 25 % to 4% [8].

Typically, diagnosis is based on the presence of the clinical signs consistent with the Kawasaki diagnostic criteria, and after the exclusion of other diseases [8,70,72]. Lack of awareness and delays in management have been documented in pediatric clinical practice [8,73].

Due to “stay-at-home” orders and the risk of novel coronavirus disease in 2019 (COVID-19), many parents hesitated or feared seeking in-person consultations for their children. This resulted to reductions in emergency department visits and hospital admissions [74]. In addition, healthcare providers have focused on COVID-19 management during the pandemic. As a result, there is significant concern that KD may have been underdiagnosed or not treated in a timely manner during the pandemic [22].

The current scientific statement endorsed by the American Heart Association incorporates new evidence regarding underlying pathological processes and suggests an algorithm to ensure identification of incomplete KD during the effective window for treatment [8]. Incomplete Kawasaki is characterized by a longer fever time, younger age of onset, a higher incidence of coronary artery aneurysms, enhanced immune tolerance to immunoglobulin or a delayed immune response compared with complete Kawasaki disease [8,73]. The higher prevalence of coronary artery lesions in incomplete KD is the result of difficulties in diagnosis due to incomplete clinical presentation, which in turn leads in delayed treatment and harm of health of the child [8,73]. Timely diagnosis and earlier treatment of incomplete KD patients could further prevent cardiovascular complications [73,75].

The diagnosis of incomplete, sometimes referred to as atypical KD, should be considered in any infant or child with prolonged unexplained fever, less than four of the principal clinical criteria, and compatible laboratory or echocardiographic findings [8,73]. Evaluation with laboratory investigations for suspected incomplete KD should be performed in children with fever ≥ 5 days and two or three clinical criteria, or infants with fever ≥ 7 days without another explanation [8]. C-reactive protein ≥ 3 mg/dl and erythrocyte sedimentation rate ≥ 40 mm/hour, if associated with ≥ 3 abnormal laboratory findings, such as anemia for the age of the child, platelets ≥ 450.000/μL after the 7th day of fever, albumin ≤ 3 gr/dl, increased alanine aminotransferase, white blood cell count ≥ 15,000/ mm^3, ≥ 10 white blood cells/high power field in the urine or an abnormal echocardiogram, identify candidates for treatment for KD [8].

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Echocardiography is considered suggestive for KD if any of the three following echocardiographic findings are met: Z score of the left anterior descending coronary artery or right coronary artery ≥ 2.5, coronary artery aneurysm or ≥ 3 other suggestive features, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z scores in left anterior descending coronary artery or right coronary artery from 2 to 2.5 [76]. This algorithm may promote early suspicion, correct diagnosis, and timely treatment of incomplete KD [73]. Incomplete disease is commonly found in infants under 12 months of age, resulting in delayed diagnoses and poor cardiac prognosis. Infants with incomplete KD seem to have a more severe disease and a greater predilection for coronary involvement than those with complete KD [77].

Misdiagnosis of KD may lead to further evolution of the disease and an increased incidence of coronary artery aneurysm, dilation of the coronary arteries, and in severe cases, myocardial infarction, or sudden death [71].

Because manifestations of KD commonly occur in other illnesses, KD may be difficult to diagnose, especially in children who present with the incomplete form of the disease [8,71,73]. The diagnosis of KD requires a high index of suspicion. Infants and children may present with subtle or incomplete clinical signs and yet still develop significant coronary artery abnormalities. Therefore, the diagnosis of incomplete KD is challenging, especially in infants presenting with unexplained fever. Primary care pediatricians must take into consideration the possibility of incomplete KD in the young pediatric patients [8,73].

7. Pulse Oximetry Screening of Healthy Newborns Prior to Discharge from the Nursery: Identification of Critical CHD in the Neonate and Missed or Delayed Diagnosis

Critical CHD represents a group of potentially life-threatening conditions, accounts for 15% to 25% of all CHD cases, and is a leading cause of infant morbidity and mortality [78,79]. In the current era, most infants with critical CHD can be managed successfully with reparative surgery or palliation. Delayed diagnosis is associated with cardiovascular compromise and organ dysfunction, resulting in poor clinical condition at the time of surgery, increased morbidity, including brain hypoxia and damage [80]. Timely diagnosis of these conditions either before or after birth can reduce the risk of acute cardiovascular collapse and death [81–83].

Most newborns with critical CHD are asymptomatic at birth [79]. Screening for CHD before 2011 involved a second trimester ultrasound scan, and postnatal clinical examination of the cardiovascular system [84]. Unfortunately, these screening methods had variable, and often low detection rates [85,86] and up to 30% of infants born with critical CHD *were discharged home before the diagnosis was established* with reported mortality as high as 50% [81,87,88]. Fetuses with abnormal findings on the obstetric screening anatomic of the mid-trimester and/or risk factors for cardiac disease should be referred for evaluation with fetal echocardiography. Fetal echocardiography should be performed by specialized sonographers and interpreted by physicians with knowledge of evolving fetal cardiac anatomy and physiology throughout gestation [63]. Although antenatal detection rates following screening ultrasonography are constantly improving over time, the average detection of isolated critical CHD remains less than 50% [86]. A meta-analysis of seven studies estimated that the pooled detection rate of CHD in unselected populations was 45.1% (95% confidence interval 33.5%-57.0%). Of course, if the postnatal clinical examination of the cardiovascular system has abnormal findings, a postnatal echocardiogram is usually performed, and the exact pathology is verified [78,89,90].

The persistence of fetal circulation after birth in a few infants can mask the clinical presentation of CHD. Thus, clinical examination abnormalities such as a heart murmur and weak and delayed femoral pulse are often absent in early postnatal life, and mild cyanosis is frequently clinically undetectable [90].

In 2009, a scientific statement from the American Academy of Pediatrics and the American Heart Association reviewed the available evidence and concluded that pulse oximetry screening may improve critical CHD detection, but evidence from larger population-based studies was required before recommending its addition to routine newborn screening [80]. In 2011 the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, the American Academy of Pediatrics,

 doi:10.20944/preprints202403.0867.v1

the American College of Cardiology Foundation, and the American Heart Association found sufficient evidence to begin screening for low blood oxygen saturation through the use of pulse-oximetry monitoring to detect CHD in well-infant and intermediate care nurseries [89]. Pulse oximetry is a simple, non-invasive, and painless tool that measures oxygen saturation, and therefore could detect critical CHD with ductal-dependent systemic or pulmonary blood flow that usually presents with hypoxemia [91].

Screening is currently performed in all healthy babies when they are at least 24 hours of age or as late as possible if the baby is to be discharged from the hospital before 24 hours of life [92]. Ways to decrease false positive screen as suggested by the Center for Disease Control are to examine the newborn while he/she is alert and when he/she is at least 24 hours old [91]. Earlier screening can lead to false-positive results [92].

Pulse oximetry screening will only identify cardiac lesions with right to left shunting and hypoxemia. Screening is recommended in the right hand and either foot. A positive screen result includes one of the following [4,91,92]:

1. Any oxygen saturation is less than 90%.
2. Oxygen saturation less than 95% in both extremities, on three measurements, each separated by one hour.
3. More than 3% absolute difference in oxygen saturation between the right hand and foot on three measurements, each separated by one hour.

A recent review of the Cochrane database concluded that pulse oximetry is a highly specific and a moderately sensitive test (sensitivity of 76.3%, confidence interval 69.5–82.0) for the detection of critical CHD with very low false-positive rates. Current evidence supports the introduction of routine screening for critical CHD in all asymptomatic newborns before discharge from the well-baby nursery [93].

Although the policy of pulse oximetry screening has been demonstrated to save lives, it is still expected that some newborns with critical CHD will be missed given the inherent limitations of this test and the variability in the clinical presentation of CHD in the newborn. That is, a negative screening result does not rule out the possibility of critical CHD [89]. Anatomic conditions with isolated outflow tract obstruction, such as pulmonic stenosis, aortic stenosis, or coarctation of the aorta, may have mild obstruction at the time screening and have normal pulse oximetry screening results [89]. Similarly, some of the conditions with complete mixing of systemic and pulmonary venous blood may have low pulmonary vascular resistance or lack significant pulmonary valve stenosis and have high pulmonary blood flow with resultant normal oxygen saturations, which may result in a passing pulse oximetry screening [89]. This explains why some infants with a single ventricle, total anomalous pulmonary venous drainage, truncus arteriosus, and hypoplastic left heart syndrome are not identified by pulse oximetry screening and can be listed as having a false negative result [89].

A model has been created for estimating the different rates of detection for each particular critical CHD [94]. Expected sensitivity of pulse oximetry for detection of critical CHD screening is high (> 80%) for critical pulmonary stenosis, d-transposition of the great arteries, hypoplastic left heart syndrome, pulmonary atresia, single ventricle, total anomalous pulmonary venous drainage, and truncus arteriosus [94]. It is medium (60-80%) for critical aortic stenosis, double-outlet right ventricle and tricuspid atresia [94]. It is low (<60%) for coarctation of the aorta, Ebstein's anomaly, interruption of the aortic arch and tetralogy of Fallot [94].

8. Discussion

The unique cardiovascular physiology of heart disease in children which is attributed to changes with growth and development from birth to adulthood is associated with differences in presenting signs and symptoms of heart disease compared to adults. This has led to the development of policies and guidelines directed towards improving the care of this population, making pediatric cardiology an exciting field of pediatrics in the current era [93].

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Major advances have been made over the previous decades in the understanding and management of pediatric heart disease with significant improvement in survival of these patients [94]. As outcome is progressively improving, children with CHD are surviving into adulthood and one of the challenges in this population is transition of care from pediatric to adult cardiologists specialized in grown-up congenital heart disease [95]. Rapid development of technology in the last decade has led to innovations in noninvasive imaging and the development of devices that are used in interventional cardiology, thus limiting the number of patients requiring diagnostic catheterization or surgery [95,96]. The collaboration between interventionists and cardiothoracic surgeons has also led to the development of hybrid interventions, which are likely to allow less invasive therapy of an increasing number of defects in the future [96].

Yet, the suspicion of heart disease in neonates, infants and children is one of the responsibilities of the general pediatrician. Primary care providers play a key role in the diagnosis, initial management, and referral for specialized cardiology opinion, as many common cardiac complaints are first identified in the primary care setting [93].

The routine well-child visits provide an opportunity for the primary care pediatrician, who follows children closely from birth to late adolescence to timely detect warning signs or symptoms of heart disease. During routine visits, a detailed medical history including cardiovascular symptoms such as chest pain, syncope, palpitations, exercise intolerance, and feeding difficulties, as well as family history of heart disease in close relatives should be obtained [97]. A thorough cardiovascular physical examination includes dynamic auscultation, palpation of the femoral pulses and blood pressure in the upper and lower limbs [98,99].

A cardiac murmur may be the first clinical sign of significant cardiac disease [100] and represents the most common condition leading to pediatric cardiology consultation [101]. Heart murmurs are mostly innocent with only approximately 1% representing cardiac pathology [102]. Personal and family history, the presence of symptoms and clinical examination findings depending on the patient's age are helpful in predicting the presence of heart disease and suggest pediatric cardiology consultation [103]. Distinguishing pathologic murmurs caused by an underlying heart defect from innocent murmurs caused by the flow of blood within a structurally normal heart can be challenging for the primary care physician and requires significant skills in clinical examination [104].

Red flags from the personal history include feeding difficulties, failure to thrive, respiratory symptoms or cyanosis, frequent lower respiratory infections associated with left to right shunting, precordial pain, syncope, exercise intolerance and in utero exposure to cardiac teratogens [99,104].

Concerning findings from physical examination include syndromic features, failure to thrive, peripheral edema, hyperdynamic precordium, delayed and weak femoral pulses, abnormal S2, intense (≥ 3/6) cardiac murmur, harsh quality of the murmur, a systolic click, a diastolic or holosystolic murmur, increased intensity of the murmur in standing position suggestive of hypertrophic cardiomyopathy, ascites, and hepatomegaly [99,105].

Chest pain in children and adolescents is a common complain leading to pediatric cardiology consultation [104]. Indeed, after murmurs, chest pain is the second most common reason for referral for pediatric cardiological evaluation [106]. Although chest pain in pediatrics is rarely cardiac in origin, cardiovascular pathology remains a concern both for the pediatricians and the family, as precordial pain usually implies significant heart disease in adults. Previous studies estimated a cardiac etiology in only 0% to 5% of children with chest pain [106]. The management of these patients due to fear about missing a potentially serious cardiac diagnosis associated with sudden cardiac death may lead to extensive investigations, several medical visits, and hospitalizations, which are often costly and unnecessary [104,105].

The etiology of chest pain in pediatrics usually involves musculoskeletal, pulmonary, gastrointestinal, as well as psychogenic etiologies [104]. Idiopathic chest pain is the most common diagnosis, the symptoms are typically chronic and laboratory testing is usually nondiagnostic [106]. Primary care physicians can be reassured that cardiac pathology is excluded when the patient history, physical examination, and electrocardiogram are normal [104]. Potential causes of cardiac chest pain include aortic pathology due to aortic dissection, pericarditis, and myocarditis, congenital and

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acquired coronary abnormalities, cardiomyopathies, severe aortic valve or subaortic obstruction and arrhythmias [103,104].

Of primary importance is identifying life-threatening causes needing acute management. Red flags increasing the suspicion that chest pain may be of cardiac origin are pain with exercise or physical activity, chest pain associated with palpitations or syncope, family history of sudden cardiac death or cardiomyopathy in first degree relatives, known history of congenital heart or Kawasaki disease and chest pain associated with electrocardiogram abnormalities [103,107].

Syncope is defined as the transient loss of consciousness and postural tone resulting from an abrupt, temporary decrease in cerebral blood flow [107–111]. One or more syncopal episodes affects approximately 15% of children younger than 18 years [111]. It is one of the most common referrals to pediatric cardiology and neurology clinics [106,109]. The age of the child is important, as it is a rare phenomenon under the age of 10 years except for breathing holding syncope [112]. There is an estimated 30% lifetime risk [112]. Sixty to 80 percent of the episodes are self-limited and benign [110]. It is not uncommon to elicit a history of multiple family members who experienced syncope during adolescence that subsequently resolved [112].

The non-life-threatening causes of syncope fall into two categories. Reflex syncope, including 'vasovagal' syncope or simple fainting is attributed to reflex (vagal) nervous activity resulting in slow heart rate and hypotension and represents the most common diagnosis [113]. Another cause is orthostatic hypotension which represents an impairment of systemic vascular resistance due to a variety of primary and secondary causes concerning the autonomic nervous system [114]. Features suggestive of reflex syncope include nausea, vomiting, after an emotionally stressful event, following prolonged standing in a hot, crowded area, during or after a meal, after exercise and head rotation [114]. Syncope due to orthostatic hypotension occurs following standing from supine, sitting or squatting position, standing after exercise, prolonged standing in a hot environment and secondary to commencement of vasoactive medications [114]. Orthostatic hypotension is defined as a decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg after three minutes of standing, compared with blood pressure in the supine or sitting position. Pulse strength, rate, and any differences between upper and lower extremities should be noted [112]. A thorough personal and family history, a detailed physical examination and possibly an electrocardiogram in children with syncope are sufficient to avoid unnecessary, extended, and expensive diagnostic investigations [108,112,114]. Most syncopal episodes in the pediatric population are diagnosed clinically or with minimally invasive testing, emphasizing the importance of a detailed history and physical examination [18]. The electrocardiogram allows screening for dysrhythmias, such as Wolff-Parkinson-White syndrome, heart block, and long QT syndrome, as well as hypertrophic cardiomyopathies and myocarditis [112]. The uncertainty generates significant anxiety to the parents and patients and can have a major impact on the patient's quality of life, can cause a major impact on lifestyle, interfering with school activities and/or sports [109,110,112]. The primary concern is generally whether or not the syncopal episode is an event that precedes sudden cardiac death or signals the onset of epilepsy [114]. Thus, accurate diagnosis and counseling are important [110,112].

The serious, life-threatening causes of syncope are generally cardiac in nature, in which case syncope can be the first warning sign of a serious condition, such as an electrical disturbance (arrhythmias) or structural heart disease [108,114]. Red flags included syncope with no prodromal symptoms, sudden collapse usually during exertion, family history of sudden unexplained death in first degree relatives, abnormal electrocardiogram involving the QT interval, a systolic murmur that intensifies with the Valsalva maneuver on physical examination suggestive of hypertrophic cardiomyopathy, gallop rhythm, and unexplained tachycardia [6,111]. Patients presenting to the pediatrician's office with concerning signs or symptoms possibly attributed to heart disease should be restricted from physical exercise and be referred for pediatric cardiological evaluation. All patients with exertional syncope, even those with positive orthostatic vital signs, should undergo evaluation with an echocardiogram and exercise testing [112].

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Palpitations are a common complaint that patients and caregivers report to their primary care pediatrician seeking medical advice. Palpitations are defined as the perceived abnormalities of the heartbeats which are described by the patient as bouncing, fast and/or irregular [115]. In their majority, they do not imply a cardiovascular abnormality. The primary care pediatrician should identify whether palpitations are secondary to an arrhythmia, with the most common diagnoses being supraventricular tachycardia, premature atrial and ventricular contractions [115].

Several important elements from the medical history are suggestive that palpitations are clinically important, such as abnormal beats which are abrupt, when the heart rate is "too fast to count", if symptoms occur at exercise and if they are associated with chest pain, shortness of breath, dizziness, or syncope. It is important to document whether palpitations last for seconds or hours and if they occur often or occasionally [115].

The 12-lead electrocardiogram may record the arrhythmia and identify pre-excitation that poses the patient at risk for arrhythmias. A Holter monitor is not useful in the evaluation of infrequent episodes of palpitations but will determine their cause if the frequency of ectopy is high [115].

A common physiologic phenomenon which is noted during routine pediatric examination as irregular heart rhythm is sinus arrhythmia. During inspiration, the vagal tone decreases resulting in increase in heart rate while during expiration the vagal tone is restored and the heart rate decreases. The heart rate change with the respiratory cycle happens because children have a strong vagal tone and high baroreceptor reflex sensitivity. This is a physiological and innocent finding that requires only reassurance [93].

There are several pathologic conditions that increase the risk of sudden cardiac arrest (SCA) or sudden cardiac death (SCD) in the young. Although significant attention has been given towards prevention of SCD in young competitive athletes with preparticipation evaluation, efforts have been made to screen the general pediatric population for potentially lethal cardiac conditions irrespective of their athletic status [116,117].

The American Academy of Pediatrics policy statement that addresses prevention of SCA and SCD includes a comprehensive review of conditions that require medical attention and pediatric cardiological referral. This policy statement proposes that the same screening that is used for athletes should also be applied to nonathletes [118]. The physician who gets mostly involved in the prevention of SCA and SCD is the primary care pediatrician who follows children regularly from birth into puberty or even young adulthood and who is in close contact with the child and caregivers for many years. Primary care pediatricians are responsible for preparticipation screening for school physical activities eligibility and are often the first called when a cardiac symptom or cardiac arrest occurs [118].

The primary care pediatrician via routine physical examination or the recognition of suspicious symptoms has the responsibility to identify patients at risk for SCA or SCD and refer to a pediatric cardiologist to perform a comprehensive cardiovascular evaluation. However, there are children who, despite the best screening efforts, still experience SCA [118]. It is of paramount importance for the primary care pediatrician to have basic knowledge of the common pathologic conditions that put young patients at risk for SCA and SCD [118]. These include cardiomyopathies, channelopathies (long QT syndrome, short QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia and idiopathic ventricular fibrillation), congenital heart disease, Wolf-Parkinson White syndrome, anomalous coronary arteries and aortopathies [118].

Fourteen elements of the personal and family history and physical examination are recommended by the American Heart Association as part of a comprehensive medical questionnaire, which are to be used as a guide to physicians performing preparticipation examination [118]:

Personal history:

1. Chest pain, discomfort, tightness, or pressure related to exertion.
2. Unexplained syncope or near-syncope, not felt to be vasovagal or neurocardiogenic in origin.
3. Excessive and unexplained dyspnea or fatigue or palpitations associated with exercise.
4. Previous recognition of a heart murmur.
5. Elevated systemic blood pressure.

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6. Previous restriction from participation in sports.
7. Previous testing for the heart, ordered by a physician.
8. Family history of premature death (sudden and unexpected or otherwise) before 50 years of age attributable to heart disease in one or more relatives.
9. Disability from heart disease in close relative under 50 years of age.
10. Hypertrophic or dilated cardiomyopathy, long QT syndrome or other ion channelopathies, Marfan syndrome, or clinically significant arrhythmias; specific knowledge of genetic cardiac conditions in family members.

Physical Examination:

11. Heart murmur, not felt to be innocent.
12. Femoral pulses to exclude aortic coarctation.
13. Physical stigmata of Marfan syndrome.
14. Brachial artery blood pressure (sitting position), preferably taken in both arms.

A positive response to any of the 14 points may prompt cardiovascular evaluation at the discretion of the primary care physician. Electrocardiogram screening has been shown to detect some cardiac lesions that pose a risk for SCA and SCD or require restriction from athletic participation [120].

In 2005, the European Society of Cardiology formally recommended and strongly promoted national screening with electrocardiograms limited to athletes [6]. The main purpose of the consensus document was to reinforce the principle of the need for pre-participation medical clearance of all young athletes involved in competitive sports programs to prevent athletic field fatalities on the basis of the proven efficacy of systematic screening by 12-lead electrocardiogram, in addition to history and physical examination [121,122]. The electrocardiogram is five times more sensitive than history and 10 times more sensitive than physical examination, and has a higher positive likelihood ratio, lower negative likelihood ratio, and lower false-positive rate than history or physical examination. The 12-lead electrocardiogram interpreted using modern criteria should be considered the best practice in screening athletes for cardiovascular disease, and the use of history and physical examination alone as screening tools should be reevaluated [122].

Controversy exists over the use of the electrocardiogram in sports pre-participation screening. A recent meta-analysis concluded that the odds of detecting both cardiac disease and conditions related to SCD with electrocardiogram are greater than with history and physical examination alone during sports pre-participation screening [120].

The discussion of such massive screening with electrocardiogram in the U.S. has been regarded as complex and is not routinely performed due to the low prevalence of cardiovascular diseases responsible for sudden death in the young population, the low risk of sudden death among those with cardiovascular diseases, the large populations who are candidates for screening, and the imperfection of the 12-lead electrocardiogram as a diagnostic test. Therefore, routine 12-lead electrocardiogram is not included in preparticipation screening of athletes in the U.S. [119].

The American Academy of Pediatrics recommends four questions directed toward SCA and SCD detection for which a positive response suggests an increased risk for SCA and SCD. In contrast to the American Heart Association recommendations, the American Academy of Pediatrics tool is intended to be used in all children regardless of athletic participation [4]. Primary care pediatricians may find a positive response to be a significant indication to perform a cardiovascular evaluation.

The four American Academy of Pediatrics screening questions based on expert opinion, are as follows [118]:

1. Have you ever fainted, passed out, or had an unexplained seizure suddenly and without warning, especially during exercise or in response to sudden loud noises, such as doorbells, alarm clocks, and ringing telephones?
2. Have you ever had exercise-related chest pain or shortness of breath?
3. Has anyone in your immediate family (parents, grandparents, siblings) or other, more distant relatives (aunts, uncles, cousins) died of heart problems or had an unexpected sudden death

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before age 50? This would include unexpected drownings, unexplained auto crashes in which the relative was driving, or sudden infant death syndrome.

4. Are you related to anyone with hypertrophic obstructive cardiomyopathy, Marfan syndrome, arrhythmogenic cardiomyopathy, long QT syndrome, short QT syndrome, Brugada syndrome or catecholaminergic polymorphic ventricular tachycardia or anyone younger than 50 years with a pacemaker or implantable defibrillator?

A positive response to the above questions or an abnormal electrocardiogram should prompt further investigation by a pediatric cardiologist [118].

According to the American Academy of Pediatrics guidelines, all children should be evaluated for conditions predisposing to SCA and SCD during the well-visits as part of the routine pediatric health care [119]. A thorough and detailed history, family history, and physical examination are necessary to assess SCA and SCD risk. The electrocardiogram should be the first test ordered when there is concern for SCA risk. It should be interpreted by a trained physician and the computer analyzer of the electrocardiogram should not be used as it is unreliable in children [118].

The American Board of Pediatrics has issued guidelines for pediatric residents on pediatric cardiology topics. At many academic institutions, the teaching on this inpatient subspecialty service is variable and may depend on the patient volume. Thus, residents may not have exposure to the American Board of Pediatrics topics during the course of their pediatric cardiology rotation [123]. A study was conducted in a single center aiming to assess pediatric residents efficacy, their comfort with American Board of Pediatrics cardiology topics, and to subsequently develop and implement a structured pediatric cardiology curriculum. Residents were re-surveyed annually for two years after the implementation of the new curriculum [123]. Seventy-six percent of residents were less than very comfortable with the differential diagnosis of cyanosis in a newborn and 92% of residents were less than very comfortable with murmur identification after their pediatric cardiology rotation. The implementation of a structured pediatric cardiology curriculum assured coverage of the American Board of Pediatrics, recommended pediatric cardiology topics during the resident rotation. Furthermore, the new curriculum improved resident comfort with pediatric cardiology patients [123].

Pediatric residents must be able to diagnose, triage, and manage infants and children with congenital heart disease [123,124]. The pediatric cardiology division at the Medical University of South Carolina updated their curriculum for pediatric residents aiming to determine if shorter lectures with more active learning with faculty and fellow participation is associated with comprehension and retention of core pediatric cardiology knowledge as demonstrated by mean test scores [124]. The results of the study showed that using an active, multimodal educational series, pediatric residents had a significant increase in mean test scores in pediatric cardiology and demonstrated good retention. This didactic strategy based on short, focused lectures and interactive workshops, aligns more with modern learning theories and supports residents as learners.

In recent years, pediatric trainees are likely less experienced in managing acutely ill cardiac patients than previous generations. This often is the consequence of the limited resident role in the care of children with critical heart disease, as they may not rotate though the cardiac intensive care unit [125]. Meanwhile, continuous progress in medical knowledge increases the material educators have to teach, thus limiting the amount of time they can devote to each area of pediatrics. The educational time they can afford should be high-impact, efficient, and engaging to optimize acquisition and retention of knowledge. Moreover, advances in prenatal diagnosis and the institution of universal neonatal pulse oximetry screening decrease the opportunities for trainees to be exposed to the diagnostic challenge of unknown congenital heart disease [126,127]. However, trainees must adapt and learn to manage these patients despite current limitations [128]. Recently, a simulation-based cardiac curriculum has been found to improve residents' ability to recognize, stabilize, and triage pediatric cardiac patients. This simulation has already been demonstrated to have beneficial association with improved clinical management of pediatric cardiology cases [128].

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8. Conclusions

In conclusion, primary care pediatricians come across and need to investigate a wide range of sometimes complex and severe clinical conditions. Therefore, the primary care setting is at risk of making medical errors [12]. Pediatric providers recognize that the children and adolescents for whom they care face risks of harm associated with delayed, missed, and erroneous diagnoses which occurs relatively frequently. The risk of diagnostic errors is markedly higher among trainees [17,129]. They endorsed inadequate data gathering, poor care coordination, and patient/caregiver-related delays as prominent contributing factors [130]. Medical errors are multifactorial in origin and incomplete history and physical examination, as well as excessive workload have also been cited as principal contributing factors for medical errors [129].

Data about diagnostic errors from pediatric practice are especially limited. Information on the most frequently misdiagnosed conditions is scarce, and little is known about which diagnostic processes are most vulnerable to failure or misclassification [130]. Presenting symptoms of the cardiac conditions described in this paper are highly variable and sometimes they did not have any obvious direct relationship to the pathology that was missing.

Errors of diagnosis occur when diagnosis is unintentionally delayed (sufficient information was available earlier, but was not appreciated), wrong (another diagnosis was made before the correct one) or missed (no diagnosis was ever made [16]. Understanding the circumstances around which these errors occur in typical primary practice is a necessary step toward generating preventive strategies. To improve diagnosis in pediatrics, it is imperative that pediatric researchers work collaboratively to identify and evaluate pediatric diagnostic errors more reliably [130].

Author Contributions: Conceptualization, A.A.K.; methodology, A.A.K.; software, A.A.K., S.F. and X.S.; validation, A.A.K., S.F., D.G. (Despoina Gkentzi), and X.S.; formal analysis, A.A.K. and N.O.; investigation, A.A.K., E.K., and G.D. (Gabriel Dimitriou); resources, A.A.K., S.F. and N.O.; data curation, A.A.K. and X.S.; writing—original draft preparation, A.A.K. and N.O.; writing—review and editing, A.A.K., S.F., D.G. (Despoina Gkentzi), E.K., N.O., G.D. (Gabriel Dimitriou) and X.S.; visualization, A.A.K., S.F., D.G. (Despoina Gkentzi), E.K., N.O., G.D. (Gabriel Dimitriou) and X.S.; supervision, A.A.K., S.F., and X.S.; project administration, A.A.K.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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