# Diagnosis and Management of Noncardiac Complications in Adults With Congenital Heart Disease

## A Scientific Statement From the American Heart Association

**ABSTRACT:** Life expectancy and quality of life for those born with congenital heart disease (CHD) have greatly improved over the past 3 decades. While representing a great advance for these patients, who have been able to move from childhood to successful adult lives in increasing numbers, this development has resulted in an epidemiological shift and a generation of patients who are at risk of developing chronic multisystem disease in adulthood. Noncardiac complications significantly contribute to the morbidity and mortality of adults with CHD. Reduced survival has been documented in patients with CHD with renal dysfunction, restrictive lung disease, anemia, and cirrhosis. Furthermore, as this population ages, atherosclerotic cardiovascular disease and its risk factors are becoming increasingly prevalent. Disorders of psychosocial and cognitive development are key factors affecting the quality of life of these individuals. It is incumbent on physicians who care for patients with CHD to be mindful of the effects that disease of organs other than the heart may have on the well-being of adults with CHD. Further research is needed to understand how these noncardiac complications may affect the long-term outcome in these patients and what modifiable factors can be targeted for preventive intervention.

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As survival to adulthood in individuals with congenital heart disease (CHD) has improved, adults with CHD are increasingly at risk for noncardiac complications.[1,2] The median age of adults with CHD has increased to 40 years, and the number of adults with CHD >65 years of age is steadily growing.[3–5] As patients age, common adult comorbidities such as diabetes mellitus (DM), coronary artery disease, and hypertension may have an impact on long-term outcomes.[6,7] Residual hemodynamic abnormalities or unrepaired CHD may place them at risk for hematologic, liver, and kidney disease. It has become increasingly important for practitioners who care for adults with CHD to understand not only the late cardiac sequelae of their patients' CHD but also the noncardiac problems that develop in adulthood. The purpose of this review is to provide a state-of-the-art update of noncardiac complications in adults with CHD.

## OVERVIEW

Extracardiac complications are increasingly prevalent in adults with CHD. The prevalence of noncardiac comorbidities such as DM and renal disease is significantly higher in a primary care population of adults with CHD compared with the general population.[8] Even adult patients with simple CHD may have a significant number

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of comorbidities, including DM, stroke, pneumonia, and renal and hepatic dysfunction.[9]

Nearly all organ systems are affected in adults with CHD, and specific populations are at particular risk. In an outpatient study of >1000 adults with CHD, an abnormal glomerular filtration rate (GFR) was noted in ≈50%.[10] Greater than 40% of adults with CHD have abnormal pulmonary function tests.[11] Both renal disease and lung disease have been associated with decreased survival in adults with CHD.[10,11] Hepatic dysfunction is an increasingly recognized complication of the Fontan procedure, but its impact remains poorly defined in other adults with CHD.[12] Genetic syndromes are commonly associated with CHD and may lead to unique endocrine and immunological complications.[13] Noncardiac causes of death in patients with Down syndrome include Alzheimer disease, respiratory infections, stroke, DM, and seizures.[14] Cyanotic patients with CHD represent some of the most complex patients, with potential complications affecting nearly all organ systems, including unique hematologic abnormalities. Finally, noncardiac complications are not limited to the physical domain. These individuals are at increased risk for psychological distress, neurocognitive deficits, and social challenges.

The presence of these noncardiac conditions affects the long-term outcomes of individuals with CHD. A recent large population study showed that pneumonia is the second leading cause of death in adults with CHD behind cardiac issues.[15] Other noncardiac causes of death in adults with CHD included cancer, hemorrhage (cerebral, pulmonary, and gastrointestinal), and cerebrovascular events.[15,16] In the German National Registry for CHD, patients who died were reported to have had more noncardiac comorbidities than living patients.[17] The most common comorbidities included renal (21%), lung (18%), and liver (6%) disease.[17] The number of adult patients with >2 noncardiac comorbidities associated with a hospitalization with CHD almost doubled between 1998 and 2010.[18] In a study of 342 adult CHD (ACHD) admissions to an intensive care unit, abnormal thyroid, creatinine, and bilirubin tests were highly predictive of both intensive care unit and hospital mortality.[19] Furthermore, comorbidities can be costly. A recent study demonstrated renal insufficiency as a primary driver of high resource use for ACHD hospitalizations, which account for only 10% of the admissions but make up one third of the total hospital charges.[20]

The impact of noncardiac comorbidities on both cardiac and noncardiac surgery is substantial. Preoperative chronic lung or liver dysfunction is a documented risk factor for increased mortality in adults with CHD undergoing cardiac operations.[21] For noncardiac surgery, adults with CHD are at increased risk of perioperative complications, perioperative mortality, longer length of stay, and higher hospital charges compared with the general population.[22] Specifically, adults with CHD undergoing noncardiac surgery are more likely to develop acute renal failure, pneumonia and respiratory failure, and deep vein thrombosis (DVT)/pulmonary embolism (PE).[22]

The approach to managing noncardiac complications in ACHD requires a multidisciplinary team with expertise in subspecialties such as hepatology, immunology, pulmonology, and nephrology, as well as familiarity with complex CHD. The creation of multidisciplinary clinics such as single-ventricle programs may allow a group of providers to monitor, manage, and possibly initiate preventive strategies to mitigate the effects of end-organ involvement in patients with CHD.[23] It is recommended that adults with CHD be evaluated and cared for in regional ACHD programs.[2] After the publication of the ACHD guidelines by the American College of Cardiology and American Heart Association (AHA),[2] the percentage of adults with CHD receiving their cardiac surgery at dedicated ACHD centers increased from 46% to 71% in California.[24] Referral to regional ACHD programs is associated with lower mortality,[25] and it is imperative that centers allocate resources to provide comprehensive care to this population. To further decrease morbidity and mortality in patients with CHD, understanding and managing noncardiac complications becomes as important as knowing their cardiac history. This review covers some of the organ systems most frequently affected in the adult with CHD (Figure 1).

## RENAL

### Prevalence

Renal dysfunction has long been described in cyanotic CHD but is common among adults with all forms of CHD.[26,27] In a study cohort of 1102 young adults with CHD, 50% had impaired renal function, with 65% of cyanotic patients having at least mild renal insufficiency (GFR, 60–89 mL·min$^{-1}$·1.73 m$^{-2}$).[10] The prevalence of significant renal dysfunction in this study (GFR <60 mL·min$^{-1}$·1.73 m$^{-2}$) was 18-fold higher in adults with noncyanotic CHD and 35-fold higher in those with cyanotic CHD compared with the same-aged general population. Patients with Eisenmenger physiology had the highest prevalence of renal dysfunction at 18%. The prevalence of renal dysfunction increases as adults with CHD age. For instance, in patients with Fontan physiology, the prevalence of mild renal dysfunction increased from 10% at 13 to >50% by 26 years of age.[10,28] In addition, renal dysfunction is associated with higher rehospitalization rates, worse surgical outcomes, and increased mortality.[4,10,27,29,30] Adults with CHD with mild renal dysfunction have a 2-fold increase in 6-year mortality, whereas patients with moderate or severe renal dysfunction demonstrate a 5-fold increase.[10]

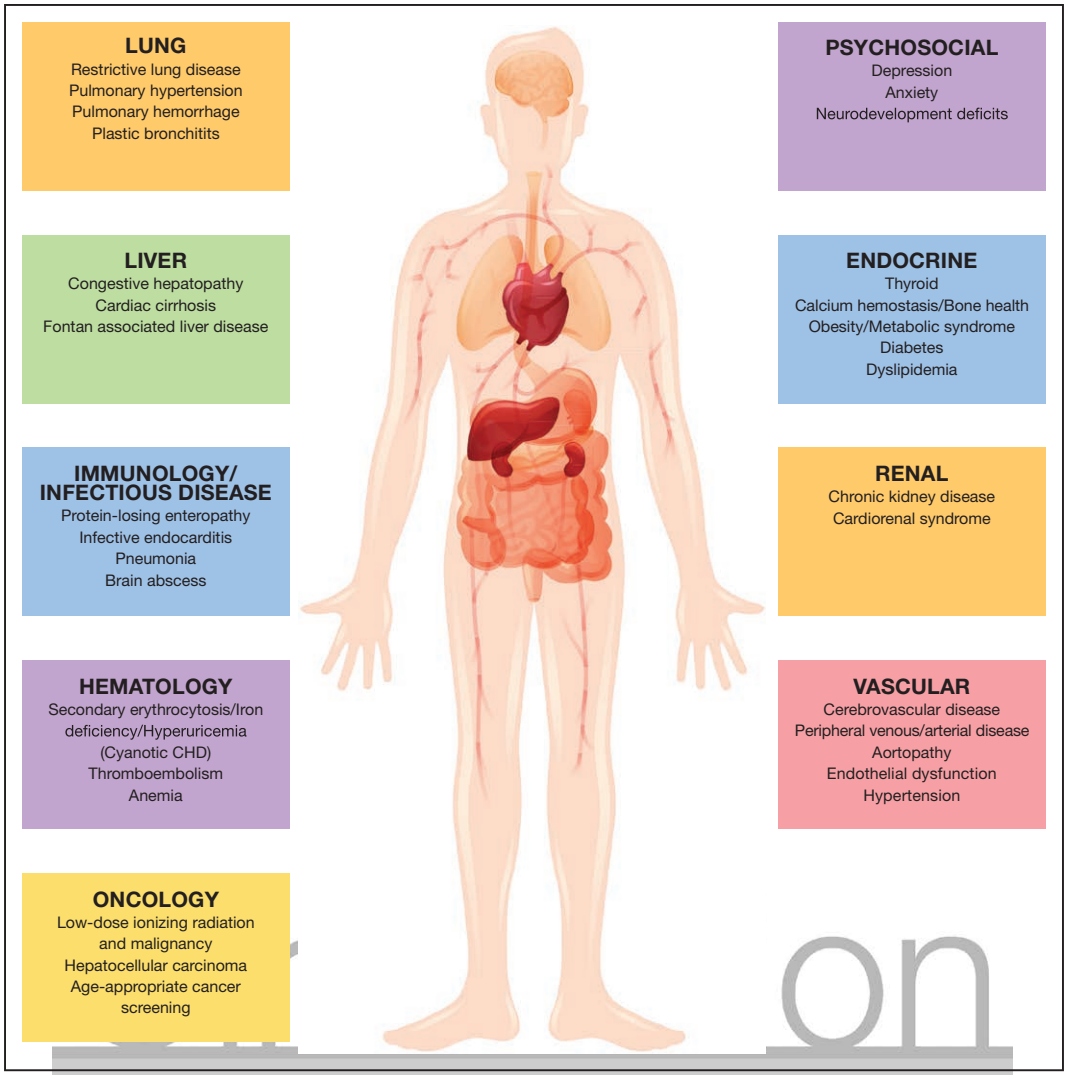


**Figure 1. Noncardiac complications in adults with congenital heart disease (CHD).**

## Pathogenesis

The heart and kidneys not only are connected by vasculature but also share a complex system of control mediated by neurohormones affecting hemodynamic parameters such as blood pressure and intravascular volume. Multiple signaling pathways communicate between the 2 organ systems, including the renin-angiotensin-aldosterone system, natriuretic peptides, and sympathetic nervous system. Renal disease has long been linked to acquired cardiovascular disease, to common risk factors such as hypertension and DM, and to chronic kidney disease (CKD)–specific risk factors such as chronic anemia, malnutrition, and vascular calcification.[31] These complex cardiac and renal interactions have been codified as cardiorenal syndromes. The most common type in the general population (type 2 cardiorenal syndrome), a condition of chronic cardiac dysfunction leading to kidney injury, is present in ≈63% of patients hospitalized with congestive heart failure[32] and occurs secondary to low cardiac output,[33] impaired renal blood flow, and renal venous congestion.[34] These factors combined lead to neurohormonal activation and impaired renal autoregulation.[35] CHD not only shares the pathophysiological hemodynamic conditions with congestive heart failure states (impaired cardiac output and increased central venous pressure) but also likely causes the same neurohormonal dysregulation that has untoward effects on the kidney.[36,37] Patients with CHD also have unique risk factors for developing renal dysfunction that occur with cardiac surgery and cardiopulmonary bypass.[38–40] Cardiovascular surgery and cardiopulmonary bypass may limit renal blood flow, causing hypoxemic-ischemic injury, and are known to stimulate aldosterone and vasopressin release. The result is a transient decrease in GFR and acute kidney injury evidenced by an elevated creatinine measurement, which may be repetitive in the case of multiple cardiac surgeries, as is common in patients with CHD. This repeated acute kidney insult is associated with the development of CKD.[41]

Congenital renal anomalies commonly coexist with CHD, may lead to CKD, and may be seen in the VACTERL and CHARGE syndromes. These syndromes consist of vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities in VACTERL and coloboma of the eye, heart defects, atresia of the choanae, retardation of growth and development, and ear abnormalities in CHARGE. A small retrospective series reported that 30% of patients with CHD also had renal anomalies.[42] Although the true prevalence is likely lower, many pediatric cardiac centers actively screen patients with complex CHD for structural renal abnormalities. Renal artery stenosis is prevalent in nonsyndromic (familial supravalvular aortic stenosis) and syndromic (Williams-Beuren syndrome) elastin insufficiency and may contribute to the development of hypertension in those individuals.[43,44] Patients with Williams-Beuren syndrome commonly develop severe hypercalcemia during infancy, although it is not clear if this promotes vascular calcification later in life.[45]

Cyanotic patients with CHD have unique risk factors for developing CKD. These include direct hypoxia leading to early renal tubular injury[46,47] and reactive erythrocytosis. This erythrocytosis induces secondary hyperviscosity leading to engorgement of the glomerular capillary beds, which in turn increases the efferent glomerular arteriolar resistance.[10,48] Eventually, glomerular shrinkage arises and leads to sclerosis. Furthermore, as a result of altered oncotic pressure dynamics in the postglomerular blood vessels, solute resorption and hence fluid retention are favored as glomerular sclerosis occurs.[48] Altered urate clearance with hyperuricemia is common in cyanotic patients; these abnormalities are usually well tolerated in the absence of gout.[49] Because of the presence of glomerular sclerosis and altered osmotic gradients, patients with cyanotic CHD may have significant microalbuminuria or proteinuria that occurs concurrently with azotemia.[50,51] The prevalence of frank proteinuria may be as high as 16% and carries clinical consequences such as increased incident thromboembolic complications.[52] In addition, cyanotic patients may develop secondary renal tubular acidosis with subsequent normal anion gap metabolic acidosis.[53]

## Management

Assessment of kidney function may be accomplished through standard methods of calculating GFR, relying on serum creatinine, age, sex, and race. Normal kidney function is defined as ≥90 mL·min$^{-1}$·1.73 m$^{-2}$. Because of the high prevalence of renal dysfunction and its indications for clinical mortality and morbidity in adults with CHD, assessment of renal function should be considered at regular intervals, particularly for cyanotic patients or those with Eisenmenger physiology,[2] with consideration for referral to nephrology. This may be accomplished through creatinine measurement (serum or 24-hour urine) with subsequent calculation of GFR[2] and performed judiciously before procedures such as cardiac catheterization when intravenous contrast use is planned and during the postoperative period.[2] Current practice suggests that cyanotic adults with CHD with a reduction in GFR have a urinalysis to assess for the presence of proteinuria via measurement of a protein-to-creatinine ratio. Another measurement of CKD that may be a better predictor of GFR than serum creatinine is cystatin C.[54–56] Unlike serum creatinine, cystatin C is not affected by age, sex, race, or muscle mass.[54] Cystatin C and urinary biomarkers such as neutrophil gelatinase-associated lipocalin, interleukin-18, liver fatty acid binding protein, and kidney injury molecule-1 have been shown to be predictors of acute kidney injury after cardiac surgery in children and deserve further study in adults with CHD.[54,57] CKD in adults with CHD prompts a review of medications known to be associated with renal dysfunction, particularly those commonly used by adults with CHD such as angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory agents, diuretics, and some antiarrhythmic medications. Use of these known nephrotoxic agents in the setting of CKD warrants careful longitudinal surveillance of renal function. Interventional and surgical procedures ought to be meticulously planned with attention paid to the preprocedural hydration status with renal protection prophylaxis (volume expansion with isotonic saline) used when indicated.[2]

# LUNG

## Prevalence

Several studies have demonstrated that adults with CHD have reduced pulmonary function resulting from restrictive lung disease compared with healthy controls.[58] Forty-four percent of adults with CHD demonstrated a pattern on spirometry suggestive of restrictive lung disease, which is markedly higher than the 9% prevalence in the general adult population.[59] The prevalence of restrictive lung disease was highest in patients with a history of Fontan procedure (89%) and tetralogy of Fallot (TOF) repair (76%).[59] Forced vital capacity and forced expiratory volume in 1 second have been shown to be reduced in adults with CHD, a finding that is highly suggestive of abnormal pulmonary mechanics.[60,61]

Other pulmonary complications such as pulmonary hemorrhage, recurrent pneumonia, and PE are more common among adults with CHD.[62] Patients with Fontan physiology are at risk for a rare but debilitating complication: plastic bronchitis. The prevalence has been estimated to be 4% in children after Fontan palliation.[63,64] Thromboembolic events, particularly PE, are associated with significant morbidity and mortality in patients with Fontan physiology.[65] Patients with TOF/







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pulmonary atresia, multiple aortopulmonary collaterals, and Eisenmenger syndrome are at risk for pulmonary hemorrhage. Hemoptysis can occur in up to 30% of patients with Eisenmenger syndrome.[66,67] Finally, pneumonia has been shown to be one of leading causes of death in adults with CHD.[16] Recurrent pneumonia in adults with CHD is discussed further in the section on infectious disease.

## Pathogenesis

Restrictive lung disease is characterized by reduced lung volumes, resulting from either an intrinsic cause such as an alteration in lung parenchyma or an extrinsic cause such as a disease of the pleura, chest wall, or neuromuscular apparatus.[58] The higher prevalence of restrictive lung physiology in adults with CHD is often secondary to an extrinsic pulmonary cause. The chest wall is an important component of normal respiratory function, and multiple thoracotomies can lead to a restrictive thoracic cage, which in turn disrupts normal chest wall mechanics and respiratory function.[58] A previous thoracotomy has been identified as a strong predictor of restrictive lung physiology.[59] Spinal deformities, including scoliosis and kyphosis, are significantly more common in patients after repair of CHD and may be related to previous thoracotomy or sternotomy.[68] Patients with TOF or Fontan physiology are likely to have undergone multiple previous surgeries and are most likely to have restrictive pulmonary mechanics.[59,61] Diaphragmatic weakness or paralysis is a sequela of congenital heart surgery that can be seen with routine chest x-ray and may further compromise respiratory mechanics. Finally, restrictive lung physiology in the adult with CHD may be related to neuromuscular causes. Respiratory and skeletal muscle weakness was common in young adults with complex CHD and similar to that found in adults with advanced heart failure from acquired disease.[69]

Intrinsic causes of restrictive lung disease include decreased pulmonary blood flow that may hinder growth and development of lung parenchyma, resulting in pulmonary hypoplasia.[70] This may partly explain the significantly higher prevalence of restrictive lung physiology in patients with TOF. Another intrinsic cause of restrictive lung physiology in adults with CHD may be pulmonary toxicity from amiodarone use.[59]

Obesity further exacerbates restrictive lung physiology in adults with CHD. Obesity has a clear impact on chest wall mechanics, may lead to a risk for further physical deconditioning with associated respiratory and skeletal muscle weakness, and is a risk for obstructive sleep apnea. Obstructive sleep apnea affects 9% to 24% of the general population.[71] Although the true prevalence of obstructive sleep apnea in the adult with CHD remains unknown, the potential detrimental effects on pulmonary physiology cannot be overlooked. These effects include hypoxia, hypoxia-induced pulmonary vasoconstriction, and ultimately, pulmonary hypertension.[71] This is particularly worrisome given that as many as 10% of adults with CHD seen in clinic at baseline have pulmonary hypertension.[67,72]

## Impact

Abnormal lung function is a common and often underrecognized cause of both long-term morbidity and mortality in adults with CHD.[11,59–61] Restrictive lung physiology in particular is a major contributor to reduced exercise tolerance and functional capacity.[59–61] Abnormal lung function, previous cardiac surgery, and low heart rate reserve were associated with reduced exercise capacity in adults with CHD.[59,61] Restrictive lung physiology likely contributes to reduced exercise tolerance by resulting in a decreased ventilator capacity and higher ventilator demand. Thus, during exercise, these patients augment their minute ventilation by increasing their respiratory rate rather than tidal volume.[73] Increased dead space ventilation, decreased vital capacity, reduced respiratory muscle strength from decreased thoracic or lung compliance, and abnormal gas exchange likely also contribute to decreased exercise tolerance in these patients.[73] Abnormal ventilatory response during exercise has been demonstrated in adults with various CHD diagnoses.[74] This is particularly true in patients with restrictive lung physiology and is evidenced by markedly elevated minute ventilation in response to incremental increases in carbon dioxide production compared with healthy adults ($\dot{V}_E/\dot{V}_{CO_2}$ slope).[74] This finding signifies that the ventilatory demand at any level of exercise for a patient with restrictive physiology is increased. In addition, there is concern for abnormal heart-lung interaction during exercise in patients with moderate restrictive lung dysfunction. Studies suggest that in the setting of restrictive lung disease, right ventricular dysfunction as a result of elevation in pulmonary pressures and reduced compliance from stiff lungs or chest wall are seen, resulting in restricted right ventricular diastolic filling during exercise.[73] At the same time, lung disease may also impair left ventricular performance. Abnormal ventilatory mechanics can alter left ventricular filling, increase left ventricular afterload, and result in reduced left ventricular function.[75,76] In addition to exercise intolerance, restrictive lung physiology has been associated with increased hospitalization, atrial arrhythmias, and mortality.[59,74] Adults with CHD who have a reduced forced vital capacity have a 1.6-fold increased risk of death compared with patients with normal lung function.[11]

## Management

An initial spirometric assessment of lung function is usually performed and followed serially to screen for

abnormal lung function in adults with CHD.[77] It can be performed as part of a standard cardiopulmonary exercise test. Although spirometry is a useful tool, its disadvantage is that it is only suggestive and not diagnostic of restrictive lung disease. Formal pulmonary function testing with body plethysmography is needed to confirm the diagnosis of restrictive lung disease by showing a reduction in total lung capacity.[78,79] Baseline and annual chest x-ray with baseline pulmonary function tests with diffusing capacity for carbon monoxide and high-resolution computed tomography (CT) as indicated can identify pulmonary disease in patients on amiodarone therapy.[80]

Effective treatment options exist for patients with restrictive lung function. Pulmonary rehabilitation with endurance training is an evidence-based, multidisciplinary, comprehensive intervention for patients with chronic respiratory disease who are symptomatic and often have impaired ability to perform their activities of daily living.[81–83] Pulmonary rehabilitation has been shown to improve exercise endurance and the quality of life in patients with restrictive lung physiology of various pathogeneses and even decrease hospital admissions.[84–86] To date, specific trials looking at the benefit of pulmonary rehabilitation in adults with CHD with restrictive lung physiology are limited. Studies of supervised pulmonary rehabilitation in the setting of pulmonary hypertension associated with CHD have been encouraging, demonstrating safety and improvement in both exercise tolerance and quality of life.[87,88] Given that the potential benefits outweigh the risks with relatively low cost, pulmonary rehabilitation may be considered in patients with moderate or severe restrictive lung physiology and exercise intolerance.

Other potentially beneficial treatment modalities in patients with moderate to severe restrictive lung disease include supplemental oxygen, nocturnal noninvasive inspiratory pressure support, and respiratory muscle training. Tobacco use is investigated during routine visits, and smoking cessation discussed. Polysomnography is recommended for the diagnosis of obstructive sleep apnea by the American College of Physicians in patients with unexplained daytime sleepiness and obesity; therefore, it is considered in adults with CHD who have risk factors for obstructive sleep apnea.[89] Finally, the presence of restrictive lung physiology needs to be taken into account when planning for interventional and surgical procedures that may require sedation or intubation or that may result in further insult to the chest wall and further alteration in respiratory mechanics.

Management of other pulmonary complications such as plastic bronchitis may require an individualized approach. Treatment of plastic bronchitis has included medical therapy (sildenafil, steroids, mucolytics, inhaled tissue plasminogen activator), interventions aimed at lowering venous pressure, and transplantation.[90] Thoracic duct ligation and, more recently, percutaneous lymphatic procedures may offer symptomatic improvement.[90] Treatment of hemoptysis in the setting of Eisenmenger syndrome or multiple aortopulmonary collaterals is generally supportive in cases of self-limited episodes. However, severe episodes may require further evaluation with chest radiography and CT to assess the extent of intrapulmonary hemorrhage.[91] Aortography and embolization of culprit vessels with or without concomitant bronchoscopy may be considered in severe or recurrent episodes[91] and to rule out infection.

# LIVER

## Prevalence

The prevalence of liver disease among patients with CHD is poorly characterized and difficult to estimate because it is likely to vary between types of CHD and because liver disease is in many cases subclinical and undiagnosed. Research to date has focused predominantly on Fontan-associated liver disease (FALD). Retrospective reviews of liver histopathology in patients with Fontan physiology consistently show near-universal fibrosis both early and late after Fontan completion.[92–95] On noninvasive imaging, 57% to 67% of patients with Fontan physiology have ultrasound abnormalities of the liver, and 72% to 100% have abnormalities on CT or magnetic resonance (MR) imaging.[96–99] Epidemiologic data are limited in other CHD populations in which routine surveillance is uncommon and recognition therefore is less likely.

Manifestations of liver disease in association with CHD range from congestive hepatopathy to fibrosis with nodular regeneration and even cirrhosis.[100] Congenital portosystemic shunt (Abernethy malformation) is an exceedingly rare condition with <100 cases reported.[101–103] It is accompanied by CHD in 22% of cases, especially in the setting of polysplenia or left isomerism, and often presents with hyperammonemia, regenerative nodular liver lesions, and hepatocellular carcinoma. There are also a handful of genetic syndromes (eg, Alagille syndrome, Fas-associated death domain deficiency, orofaciodigital syndrome) of which primary liver disease and CHD are both features. Alagille syndrome, which is associated with cholestatic liver disease and cardiac anomalies such as pulmonary artery stenoses, hypoplasia, and atresia, as well as TOF and coarctation of the aorta (CoA), is perhaps the most common of these, affecting roughly 1 in 30 000 to 50 000 live births.[104]

## Pathogenesis

Contributing causes of liver disease in the ACHD population can be divided broadly into 2 categories: those







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**Table 1. Types of Heart Disease That May Be Associated With Liver Disease**

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| Right-sided heart disease |
| Fontan physiology |
| TOF with residual pulmonary regurgitation |
| Complete transposition of the great arteries after atrial switch surgery |
| Pulmonary valve disease |
| Ebstein anomaly and other tricuspid valve disease |
| Eisenmenger syndrome |
| Pulmonary hypertension |
| Pericardial disease |
| Left-sided heart disease |
| Left ventricular outflow obstruction |
| Mitral valve disease |
| Ischemic and nonischemic cardiomyopathy |
| Cor triatriatum |

TOF indicates tetralogy of Fallot.

related to hemodynamic derangements (ie, venous congestion, ischemic injury) and those related to nonhemodynamic factors (ie, viral hepatitis, drug-induced liver injury).

The unique circulation of the liver makes it especially vulnerable to injury in the setting of abnormal hemodynamics. As much as 70% of the blood supply of the liver is made up of nutrient-rich but oxygen-poor portal venous blood from the splanchnic circulation. Within the liver parenchyma, blood flows radially from the hepatic arterioles and portal venules through the sinusoids and into central veins, which coalesce and drain into the inferior vena cava. As the blood moves through the sinusoids, hepatocytes extract nutrients and oxygen. Thus, the hepatocytes closest to the central veins receive blood with the lowest oxygen and nutrient content and are most susceptible to injury from ischemia and congestion.[105]

Studies of patients without CHD show that decompensated heart failure results in compromised hepatic blood flow and therefore is associated with a greater risk of liver injury. However, decreased hepatic blood itself is rarely sufficient to cause liver injury. Rather, the combination of elevated central venous pressures and decreased cardiac output appears to be critical.[106,107] A classic example of this combination is the single-ventricle anatomy palliated to Fontan circulation. Patients with repaired TOF with residual pulmonary regurgitation, Ebstein anomaly with severe tricuspid regurgitation, complete transposition of the great arteries with obstructed systemic venous baffles, and Eisenmenger syndrome can also be affected by this combination of hemodynamic disturbances (Table 1). Left-sided heart disease can also lead to hepatic congestion as a result of pulmonary congestion and subsequent elevation of central venous pressures. Acute hemodynamic disturbances during or after cardiac surgery can result in injury that may affect long-term liver health.[108] Finally, coagulation abnormalities have been described in children with cyanotic heart disease.[109–111] Chronic hypoxemia, sluggish flow in the hepatic microcirculation, and intrahepatic sinusoidal thrombosis all may contribute to ischemic hepatic injury in this setting.[112]

Although the risk of exposure to the hepatitis C virus through blood transfusion in the current era is only ≈1 in 2 million, it was not until mid-1992 that testing methods became sensitive enough to virtually eliminate the hepatitis C virus from the national blood supply. Therefore, chronic hepatitis C infection remains an important cause of liver disease in older patients with CHD. Studies of patients with CHD who underwent heart surgery before 1992 demonstrate hepatitis C virus exposure in 8.6% of patients and chronic infection in 4% to 5% of patients.[113,114]

In cases of frequent transfusion, iron overload can lead to cirrhosis, but this is not a common scenario among patients with CHD. More often, there may be medications used to treat arrhythmias (eg, amiodarone) or pulmonary vascular disease (eg, bosentan) that have hepatotoxic potential. Although these drugs are not contraindicated, appropriate consideration and surveillance are undertaken before these medications are started and while the patients are receiving treatment, particularly in patients with known advanced fibrosis or cirrhosis.

## Management

The key to management of liver disease in adults with CHD is early detection. Because of the paucity of strong evidence, the best strategy for the diagnosis and surveillance of liver disease remains unclear, and screening for liver disease in asymptomatic patients remains controversial.[115] Table 2 adapts the recommendations from the American Association for the Study of Liver Diseases and US Preventive Services Task Force for adults with CHD.

It is recommended that clinicians inquire about jaundice, nausea, vomiting, abdominal pain, and abdominal distension as part of the routine history. An abdominal examination for hepatomegaly, splenomegaly, ascites, and right upper quadrant tenderness is performed as part of the routine physical examination at each cardiac visit, particularly for patients with CHD at risk for liver disease.[12,118,119]

Abnormalities in biochemical laboratory values are common, particularly in patients with Fontan circulation, but tend to be mild for the vast majority of patients until their liver disease becomes advanced.[120] Abnormalities in transaminases, bilirubin, protein, and clotting factors are more common in patients with heart

**Table 2. Consideration for Liver Surveillance in Adults With CHD**

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| Physical examination for signs of liver disease. Signs can include an increased liver span consistent with hepatomegaly, splenomegaly, jaundice, right upper quadrant pain, or ascites. |
| Laboratory tests, including transaminases, GGT, alkaline phosphatase, bilirubin, albumin, total protein, INR, creatinine, and platelets every 1 to 2 y in patients with CHD at risk for liver disease, including all patients with Fontan circulation starting from 5 y after Fontan completion with frequency of testing increasing at 15 y after Fontan. |
| All patients who underwent heart surgery in or before 1992 should be screened for chronic hepatitis B and C infection.[116] |
| All patients with evidence of liver disease should be vaccinated against hepatitis A and B. Those previously vaccinated against hepatitis B should have serologies checked because some patients exhibit waning immunity in adulthood.[117] |
| Imaging of liver by ultrasound, MRI, or CT should be considered in patients with abnormal laboratory studies or signs of advanced liver disease.[115] It is reasonable to perform baseline abdominal imaging in patients with Fontan physiology 5 y after Fontan completion regardless of the presence of other abnormal findings. |
| Liver biopsy may assist in staging hepatic fibrosis and diagnosing cirrhosis but is susceptible to sampling error. Liver biopsy remains important in the evaluation of nodules seen on hepatic imaging in patients with liver disease caused by CHD. |

CHD indicates congenital heart disease; CT, computed tomography; GGT, γ-glutamyltransferase; INR, international normalized ratio; and MRI, magnetic resonance imaging.

failure and in those with a combination of congestion and hypoxemia. In patients with only congestion or only hypoxemia, abnormal serum tests are seen less frequently. There has been interest in using biochemical markers of hepatic fibrosis (eg, hyaluronic acid, Forns index, FibroSure, or FibroTest) to screen for liver fibrosis in lieu of biopsy. However, most of these have been developed and validated to predict cirrhosis or advanced fibrosis for patients with hepatitis C and may or may not be useful for screening for liver disease in patients with CHD.[121–124]

Baseline laboratory studies to evaluate liver health are performed in patients with clinical evidence of liver disease or considered to be at risk for liver disease; that is, individuals with central venous hypertension or impaired cardiac output. This would include all patients with signs or symptoms of congestive heart failure and all patients with Fontan physiology starting 5 years after Fontan completion. These baseline liver studies include aspartate transaminase, alanine transaminase, γ-glutamyltransferase, alkaline phosphatase, bilirubin, albumin, total protein, and international normalized ratio, in addition to complete blood count and basic metabolic panel. It is recommended that patients with evidence of liver disease and all patients who underwent cardiac surgery in or before 1992 have serologies checked for hepatitis B and C. Frequency of subsequent testing should be individualized on the basis of clinical status.

Ultrasound, MR, and CT imaging offer greater sensitivity for assessing liver disease. Advantages and disadvantages of each modality are summarized in Table 3. MR imaging and CT imaging of the liver generally demonstrate superior sensitivity and specificity compared with ultrasound but are considerably more expensive and may have a higher false-positive rate. In addition, regular CT imaging could result in significant exposure to ionizing radiation over the course of a patient's lifetime. Findings such as irregular liver contour, atrophy of the right liver lobe and medial segment, hypertrophy of the lateral segment and caudate lobe, heterogeneous enhancement of the liver parenchyma, and regenerative nodules may signal more advanced liver disease.[125] In addition, extrahepatic findings such as splenomegaly, ascites, or collaterals and varices may offer additional prognostic value.[126]

Any concerning changes on physical examination or laboratory testing are a prompt for imaging of the liver, preferably with MR. Whether to image the liver in an asymptomatic patient who is at risk for liver disease but without examination findings or serological tests suggestive of liver disease is open to debate. For patients with Fontan circulation who are at particularly high risk for liver disease, it is reasonable to perform baseline abdominal imaging starting 5 years after Fontan completion regardless of the presence of other abnormal findings. The frequency of subsequent abdominal imaging is based on individual patient status, but it should occur no less frequently than every 3 to 5 years. In patients with CHD at highest risk for liver disease, including all patients with Fontan physiology once they have reached 15 years after the completion of the Fontan procedure, abdominal imaging should be considered every 1 to 3 years.

Because hepatocellular carcinoma (HCC) has been reported in patients with long-standing heart disease, especially in those with Fontan circulation (see Oncology), more frequent imaging for nodules is an important component of surveillance in those with more advanced liver disease.[127–131] MR imaging with a hepatocyte-specific contrast agent has emerged as the preferred imaging modality for characterization of liver masses but may not be an option in the substantial subgroup of patients with CHD with pacemakers or defibrillators and may be limited in those with coils, vascular plugs, or other metallic devices.[132] Newer contrast-enhanced ultrasonography techniques recently have been approved for use in the United States and may increase the diagnostic accuracy of ultrasound for characterizing focal liver lesions.[133]

In any patient found to have advanced liver disease or cirrhosis (ie, those with laboratory evidence of liver disease, extrahepatic signs of "portal hypertension," or significant abnormalities on imaging), abdominal imaging by ultrasound or MR is performed every 6 months in conjunction with follow-up by a hepatologist to monitor the development of hepatocellular carcinoma.[134] The combined use of serum liver tumor marker α-fetoprotein (AFP) and ultrasound increases detection rates for HCC in cirrhotic patients without CHD[135] but

**Table 3. Advantages and Disadvantages of Imaging Modalities for Detection of Liver Disease and Screening for HCC in Patients With CHD**

| | Advantages | Disadvantages | Additional Notes |
|---|---|---|---|
| Ultrasound | Inexpensive<br>Widely available<br>Highly sensitive for differentiating cystic and solid lesions<br>No ionizing radiation | Low sensitivity for detecting focal, solid liver lesions, particularly in the setting of diffuse disease<br>Often unable to detect lesions <1 cm in size<br>Low specificity<br>High operator dependency | Use of contrast agents may improve characterization of hepatic tumors<br>Useful for guiding liver parenchymal and some focal mass biopsies<br>Elastography may overestimate degree of fibrosis and may not be useful for screening in CHD |
| CT | Best spatial resolution (submillimeter resolution) | Exposure to ionizing radiation dose<br>Low sensitivity for detecting and characterizing lesions <1 cm in size<br>Contrast contraindicated in renal failure<br>Diffuse liver disease and fatty infiltration limit sensitivity for lesion detection | CT-guided liver mass biopsy useful in cases when ultrasound visualization is poor |
| MRI | High lesion-to-liver contrast<br>High spatial resolution<br>Better lesion detection and characterization than CT<br>No ionizing radiation<br>Unenhanced MRI superior to unenhanced CT | Contrast relatively contraindicated in renal failure (eGFR <30 mL·min$^{-1}$·1.73 m$^{-2}$)<br>High cost<br>Long scan time<br>Need for longer breath-holds<br>Less widely available<br>Unable to be used with many pacemakers and defibrillators | Hepatobiliary contrast media useful in characterizing specific liver tumors |

CHD indicates congenital heart disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; and MRI, magnetic resonance imaging.





also increases costs and is not recommended by the American Association for the Study of Liver Diseases for routine screening.[134] However, AFP in conjunction with imaging, particularly when a suspicious lesion is identified, may improve specificity for HCC in patients with liver disease specifically related to CHD and is reasonable to consider. Traditionally, liver biopsy has been considered the gold standard for staging hepatic fibrosis and for diagnosing cirrhosis and HCC. Histologically, the typical findings of liver disease associated with CHD are sinusoidal dilation, hepatic fibrosis coalescing into septa, and regenerative nodules. Cardiac cirrhosis refers to the condition in which bridging of adjacent central veins by fibrotic septa creates the appearance of "reverse lobulation" in which islands of relatively normal liver parenchyma surround a centrally located portal tract. This is in contrast to typical cirrhosis in which fibrous septa arise from and connect adjacent portal tracts.[136] Recently, however, the reliability and reproducibility of biopsy results have come into question. Intraobserver and interobserver variability has been demonstrated in multiple disease processes, and the patchy nature of fibrosis in congestive hepatopathy may be particularly susceptible to sampling error.[95] This may explain the poor correlation that has been described between histology and imaging findings, laboratory studies, and clinical outcomes in several studies of liver disease in patients with Fontan physiology.[94,95,99] Because of this, routine liver biopsy remains controversial, and consultation with a hepatologist may be helpful to weigh the pros and cons. However, targeted liver biopsy still plays an important role in the evaluation of nodules seen on hepatic imaging in patients with liver disease resulting from CHD because differences in hepatic blood flow from the patient's hemodynamic abnormalities may affect contrast uptake and enhancement and make accepted imaging characteristics of malignant nodules on CT and MR less reliable in this population.

Elastography, which can be performed with ultrasound or MR, is a noninvasive method for measuring liver stiffness that has been validated for the detection of advanced hepatic fibrosis in a host of liver diseases, although not specifically in congestive hepatopathy. Studies using a variety of methods have consistently shown increased liver stiffness in patients with CHD and non-CHD heart failure. However, these measurements likely overestimate the degree of liver fibrosis caused by hepatic congestion.[137–139] Thus, there is insufficient evidence to recommend routine elastography for surveillance of liver disease in the management of patients with CHD.

Generally, patients with cirrhosis undergo routine esophagoduodenoscopy to screen for esophageal varices at the time of diagnosis of cirrhosis and every 1 to 3 years thereafter.[140] Guidelines recommend nonselective β-blockers such as nadolol or propranolol for patients found to have esophageal varices to lower portal pressures, thereby reducing the risk of variceal bleeding. In practice, although varices can be seen in patients with liver disease related to CHD, the incidence of variceal bleeding appears to be quite low as indicated by limited

data. In patients with Fontan physiology, documentation of an increased hepatic vein pressure gradient is relatively rare.[95] Therefore, the decision of whether to perform esophagoduodenoscopy is made with the input of a hepatologist on a case-by-case basis.

Management of liver disease in patients with CHD must focus on modification of the underlying hemodynamic derangements (ie, hepatic congestion and decreased cardiac output). It is recommended that hepatic venous pressure gradient be measured routinely during cardiac catheterization for any patients at risk for liver disease. The status of the liver is considered when the timing of cardiac interventions is determined. For example, cirrhosis and portal hypertension in patients without CHD predict additional complications after cardiac surgery, ventricular assist device placement, and cardiac transplantation. Therefore, the presence of cirrhosis or portal hypertension may adversely influence a patient's candidacy for heart transplantation.[141–146] Heart and liver transplantation has been reported in carefully selected patients with Fontan physiology.[147]

Preventive strategies include confirmation of hepatitis B immunity in patients who have undergone vaccination previously and immunization for hepatitis A and B for those who are not currently immune. Any patients found to be chronically infected with hepatitis C are referred for possible antiviral therapy. Patients are counseled to minimize alcohol intake and to maintain a healthy weight. Clinicians are reminded to use caution when considering potentially hepatotoxic drugs. Finally, identification of and collaboration with local or regional hepatologists with specific interest and expertise in CHD-related liver disease are essential.

# IMMUNOLOGY AND INFECTIOUS DISEASE

## Protein-Losing Enteropathy

### *Prevalence and Pathogenesis*

Protein-losing enteropathy (PLE), defined as the abnormal loss of serum proteins from the gut, is seen in 5% to 15% of patients with a single ventricle after the Fontan operation.[148–151] A high level of clinical suspicion for PLE in patients with Fontan physiology is important because many patients remain asymptomatic during early stages of the disease. Others may present with chronic diarrhea or with secondary manifestations of hypoalbuminemia such as peripheral edema, ascites, clotting abnormalities, or recurrent infections. The diagnosis can be difficult in adult patients with Fontan physiology who may have other causes for edema, ascites, or hypoalbuminemia. The gold standard for diagnosis of PLE is demonstration of elevated fecal α-1 antitrypsin, an endogenous marker for blood proteins in the intestinal tract. Patients with PLE generally have α-1 antitrypsin clearance values >50 mL/24 h or a spot fecal α-1 antitrypsin concentration >100 mg/mL.[152] Additional systemic complications include growth retardation, hypocalcemia, osteopenia, thromboembolism, and infections. Immune abnormalities associated with PLE include hypogammaglobulinemia (especially immunoglobulin $G_2$,[153] lymphopenia,[154] and selective CD4 lymphocyte deficiency).[155] As a result of the combined effect of reduced lymphocytes and immunoglobulins, patients with Fontan physiology have been said to have a clinical phenotype akin to combined immunodeficiency. However, the clinical importance of these immune abnormalities is unclear, with no major opportunistic infections reported to date.[156,157] The pathophysiology of PLE is not well understood, although factors known to play an important role include chronic venous hypertension,[150] low cardiac output, increased mesenteric vascular resistance,[158] endothelial dysfunction, inflammation,[159] and loss of intestinal cell membrane integrity.

### *Management*

PLE treatment varies widely but can been broadly categorized as intestinal directed therapies, cardiac directed therapies, and extracardiac directed therapies.[150,160] The treatment of PLE typically requires multiple strategies, but the efficacy of each treatment strategy remains unknown. Intestinal therapies comprise a low-fat/high-protein diet and medium-chain triglycerides, which act to reduce intestinal lymphatic flow and fluid losses. As PLE progresses, intestinal losses can exceed dietary intake. When diarrhea is severe and oral intake is poorly tolerated, parenteral nutrition may be considered, although thromboembolism and line sepsis are significant risks. Pharmacological strategies directed at reducing intestinal inflammation and protein losses include heparin[161,162] and steroids.[158,163,164] Long-term steroid therapy requires close monitoring and treatment of side effects such as depression, osteoporosis, infection, adrenal insufficiency, and DM.[165] Periodic serum albumin infusions with diuretics may provide short-term relief of symptoms but rarely offer resolution of PLE. Finally, intravenous immunoglobulin therapy may be considered in patients with PLE and severely reduced immunoglobulin levels.[166] Cardiac directed therapies include the use of surgery and catheter-based techniques for relief of Fontan obstruction, valve regurgitation, and atrial arrhythmias.

Transcatheter fenestration creation in the Fontan circuit may lower Fontan pressures for the short term,[167] although spontaneous closure and PLE recurrence are common.[168] Fontan fenestration adds a risk of thromboembolism to the patient. Pharmacological agents used to lower Fontan pressures include phosphodiesterase type 5 inhibitors[169] and inhaled prostacyclins. Extracardiac therapies include treatment of comorbid respiratory disease, obstructive sleep apnea, and high-output

states (anemia, thyroid dysfunction, sepsis). Cardiac transplantation leads to resolution of PLE in most[170] but not all patients. It has been shown that patients with failed Fontan circulation and impaired systolic function do better after transplantation than those with failed Fontan but preserved systolic function.[171] Concern surrounding high posttransplantation mortality in patients with Fontan physiology[172–174] has meant that transplantation is currently being offered to a highly select group of patients. Although older studies reported 5-year survival of only 50% after a diagnosis of PLE,[149,167] a more recent 2014 study reported 5- and 10-year survival of 88% and 72%, respectively,[150] suggesting that PLE outcomes have improved in the contemporary era or that the disease is diagnosed earlier in its course.

Despite receiving vaccination in childhood, patients with Fontan physiology with PLE often have nonprotective titers to the measles, mumps, and rubella and hepatitis B vaccinations, suggesting loss of immunity. Patients who do not have protective titers to hepatitis B may undergo repeat vaccination. Live vaccination with measles, mumps, and rubella is not recommended.

## Infectious Disease

### Prevalence

Patients with CHD have increased risks for complications of infectious diseases compared with the general population. Complications from infection are frequently direct manifestations of infections attacking cardiovascular structures made vulnerable from defective development or surgical interventions. In addition to structural heart disease, many patients with CHD are further predisposed to increased infection-related morbidity and mortality as a result of persistent circulatory and immune dysfunction. The risk of infection persists lifelong,[175] with even small unoperated ventricular septal defects having a risk of infective endocarditis (IE) that is 20 to 30 times that of the general population.[176] The increased lifetime risk of IE in most forms of CHD means that secondary antibiotic prophylaxis is important when contemplating extracardiac bacteremia-inducing procedures.[177] Cyanotic patients with CHD are also at higher risk for infections, particularly IE, pneumonia, and brain abscesses, and are another population in whom IE prophylaxis is paramount.

Patients with heterotaxy have abnormal arrangement of the thoraco-abdominal organs across the left-right axis of the body and a high prevalence of CHD. As a result of absence or hypofunction of the spleen, patients with heterotaxy are susceptible to infection with encapsulated bacteria; one quarter will experience significant sepsis by adulthood.[178,179] Primary ciliary dyskinesia is often associated with heterotaxy syndrome, which may further increase the susceptibility of patients with CHD to respiratory infections.[180] Examples of encapsulated bacteria are *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, *N meningitidis*, group B streptococcus, *Klebsiella pneumoniae*, *Salmonella typhi*, and *Escherichia coli*. *K pneumoniae* and *E coli* are the principal pathogens in patients <6 months of age, whereas *S pneumoniae* and *H influenzae* have been the predominant pathogens in patients >6 months of age, although successful *H influenza* vaccination is altering this picture. Sepsis-related mortality is high and ranges from 27% to 82%.[179,181–184]

### Pathogenesis

There is a rising incidence of IE in transcatheter pulmonary valve replacement.[185] The incidence of IE in transcatheter pulmonary valve replacement (incidence of 3%/patient-year) may be even higher than that associated with traditional surgical approaches to pulmonary valve prosthesis.[186] Such concerns require ACHD clinicians to carefully select patients for whom transcatheter pulmonary valve replacement is appropriate and to properly prepare them for the procedure just as they would prepare a patient before surgical pulmonary valve replacement. In addition to the rising concerns surrounding transcatheter pulmonary valve replacement, recent insights into the changing microbiology of organisms associated with infections in patients with CHD require mention. *Staphylococcus aureus* still represents the most significant cause of morbidity among patients with CHD of all ages, but chlorhexidine-tolerant organisms have been noted with increasing prevalence in children with CHD and are likely to be found in the ACHD population.[187]

The use of extracardiac vascular grafts is not uncommon in patients with CHD, particularly in those who have had complex aortic arch treatment in childhood and those who need primary aortic aneurysm treatment with or without simultaneous aortic valve replacement. Patients with Marfan syndrome or those in whom the Ross operation for left ventricular outflow obstruction has been performed are noteworthy in this regard. A recently published AHA scientific statement reviews extracardiac vascular graft and endovascular infections, noting serious life-threatening infectious complications such as sepsis, anastomotic suture line disruption, mycotic emboli[188] and even death. The most common pathogenesis is intraoperative seeding of the graft by staphylococci, *Pseudomonas* species, or Gram-negative bacteria, but extracardiac graft infection can also occur as a result of wound infection or invasive procedures occurring at sites distant from the initial graft procedures, presumably by hematogenous spread. Extracardiac graft infection can be difficult to diagnose and requires a high degree of suspicion in patients who may have had vascular graft procedures months or years before clinical presentation. A full suite of imaging is usually required (echocardiography, MR, CT, positron emission tomography) to diagnose

**Table 4. Immunology and Infectious Disease Management in Patients With ACHD**

| |
|---|
| Pretreatment cultures of blood and sputum are of particular importance in ACHD, especially, but not exclusively, for those with associated immune compromise such as asplenia. Empirical use of antibiotics should be limited. |
| Fluoroquinolone treatment or combinational macrolide and β-lactam therapy should be considered even for outpatient therapy and is even more strongly recommended for pneumonia and inpatient ICU treatment. |
| Pneumococcal polysaccharide (every 5 y) and meningococcal vaccination is recommended if there is any functional cardiovascular impairment or if there is any associated immune incompetence (eg, functional asplenia).[117,190–192] |
| Tdap vaccination may be considered once in adulthood for patients with heart disease.[117] |
| Influenza vaccination is recommended every year.[117] |

ACHD indicates adult congenital heart disease; ICU, intensive care unit; and Tdap, tetanus, diphtheria, and acellular pertussis.

site involvement and complications in what often is an emergent setting.

Of the more common serious infectious disease issues facing adults with CHD, community-acquired pneumonia stands out, both because of its frequency in otherwise healthy adults and in view of the availability of effective strategies for its prevention. As previously mentioned, pneumonia is the most common noncardiac cause of death in adults with CHD, which is likely related to associated genetic disorders, associated immune compromise, or congenital abnormalities of the lung.[15] The other infection that stands out in adults with CHD is peritonitis, although no specific correlative or pathogenic findings have been documented. In the report from the CONCOR registry (Congenital Corvitia) of patients with CHD in the Netherlands, excess mortality was found in patients with ACHD compared with the general population, and among the causes, peritonitis was second only to IE as an infectious cause of death. This statistical finding was not related to any specific pathophysiological mechanism[175] but reminds clinicians of the need for careful consideration of peritonitis when evaluating a patient with CHD for possible systemic infection.

### *Management*

The Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of infectious disease in adults[189] highlight several considerations that are relevant for the ACHD population and are summarized in Table 4. Asplenic patients with fever or rigors should be advised to seek urgent medical evaluation. Daily antibiotic prophylaxis is recommended in asplenic children until 5 years of age.[193] In contrast, antibiotic prophylaxis is not recommended in asplenic adults.[194] Exceptions to this include adults with a history of severe pneumococcal sepsis, hypogammaglobulinemia, HIV, advanced liver disease, or history of transplantation. Immunocompromised adults receive amoxicillin or penicillin 250 to 500 mg twice daily, adjusted according to body weight. Alternatives to penicillin vary by age and allergic history. Patients with heterotaxy with anatomic or functional asplenia should be vaccinated against *Neisseria meningitidis, H influenzae*, and *S pneumoniae*. In the clinical setting, influenza vaccine yearly and pneumococcal vaccine every 5 years are considered in all patients with CHD, especially those with heterotaxy. Current updated immunization schedules are reviewed elsewhere.[117,190–192]

## HEMATOLOGY

Hematologic abnormalities in CHD include anemia in patients with heart failure, erythrocytosis in cyanotic CHD, and coagulation abnormalities in patients with Fontan physiology. Anemic patients with CHD have increased mortality, even after accounting for functional class, renal dysfunction, and anticoagulation use, similar to what has been found in acquired heart failure.[195–197] Erythrocytotic patients are at risk for hyperviscosity complications, and those with coagulation abnormalities are at risk for hemorrhage and thrombosis.



### Cyanotic CHD: Secondary Erythrocytosis and Iron Deficiency

#### *Prevalence*

Patients with cyanotic CHD with adequate iron stores will have secondary erythrocytosis. Iron deficiency is common in patients with cyanotic CHD. The prevalence of iron deficiency depends on the definition used but is several-fold higher than found in the general population. In a study of patients with Eisenmenger syndrome (mean oxygen saturation, 84±8%), 22% were iron deficient (ferritin level <15 ng/mL or transferrin saturation <15%), and a history of phlebotomy was strongly associated with the presence of iron deficiency. In another sample of patients with Eisenmenger syndrome, 37% were iron deficient (ferritin level <20 ng/mL).[198,199]

#### *Pathogenesis*

Secondary erythrocytosis is an important adaptation to chronic cyanosis that allows adequate oxygen delivery in the setting of decreased oxygen tension.[200] In patients with adequate iron stores, the degree of erythrocytosis is inversely related in a linear fashion to the average oxygen saturation.[201–203] Rather than secondary erythrocytosis being considered a primary problem that needs treatment, it is a physiological marker of disease severity with attendant complications that may require management.

Erythrocytosis raises concern because of its associated hyperviscosity; however, secondary erythrocytosis causes less severe hyperviscosity than polycythemia vera, a myeloproliferative neoplasm in which all cell







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lines are elevated. Blood viscosity is affected by multiple factors, including hemoglobin, hematocrit, packed cell volume, plasma viscosity, body temperature, and shear stress. Hematocrit is a stronger determinant of viscosity than hemoglobin.[204,205]

### Management

Hyperviscosity symptoms include headache, visual changes, myalgia, mucosal bleeding, and fatigue. Although blood viscosity is increased in patients with erythrocytosis, the relationship among hematocrit, viscosity, and symptoms is more complex. There is no specific hematocrit at which symptomatic hyperviscosity occurs; therefore, there is no indication to target a particular hematocrit level in patients without symptoms of hyperviscosity. Patients with cyanotic CHD should have annual testing that includes a complete blood count and assessment of iron stores.[2] Patients with symptoms of hyperviscosity are managed initially with oral or intravenous hydration. If hydration is ineffective at relieving symptoms, alternative explanations for the symptoms should be sought; patients with headaches or neurological symptoms have brain imaging to exclude abscess, and patients with joint complaints are evaluated for gout. Prophylactic phlebotomy to prevent symptomatic hyperviscosity is not recommended because it induces iron deficiency, reduces exercise tolerance, lowers oxygen-carrying capacity, and increases risk of cerebrovascular events.[198,205–207] Phlebotomy provides only transient relief of hyperviscosity symptoms; therefore, there are only 2 indications for phlebotomy: severe refractory hyperviscosity symptoms and preoperative phlebotomy for autologous blood donation if the hematocrit level is >65%.[208]

The diagnosis of iron deficiency in cyanotic CHD requires checking iron, ferritin, and transferrin saturation levels. Annual screening with these tests is recommended. Hypochromia and microcytosis, typical findings in iron deficiency, are rare in patients with cyanotic CHD because chronic cyanosis causes macrocytosis.[199] Microhematocrit centrifugation results in plasma trapping and falsely raises hematocrit, so testing should be performed with automated electronic particle counts.[205] Iron deficiency is treated to improve the associated relative anemia that inhibits oxygen-carrying capacity, leading to reduced exercise performance, fatigue, headache, or restless leg syndrome.[205] Concerns about uncontrolled erythrocytosis do not preclude iron repletion, which is done with periodic monitoring of iron levels and hematocrit. In a prospective study of iron repletion in patients with Eisenmenger syndrome, 150 to 200 mg elemental iron daily was safe and beneficial; despite an increase in hemoglobin from 19 to 20.4 mg/dL, there was no increase in symptomatic hyperviscosity. Iron supplementation improved 6-minute walk distance from 372±85 to 402±75 m and improved functional class.[209] This improvement in walk distance is similar to that seen with advanced therapy for pulmonary arterial hypertension.[210] Patients with higher baseline hematocrit had smaller increases in red blood cell counts; therefore, no baseline hematocrit is considered too high for iron repletion. Diagnosis and treatment algorithms for iron deficiency in Eisenmenger syndrome have been published.[209,211] Oral iron replacement is cost-effective and widely available but can be limited by gastrointestinal side effects such as nausea and constipation. Intravenous iron replacement is more effective but carries the risk of anaphylaxis.

## Hyperuricemia and Gout

### Prevalence and Pathogenesis

Hyperuricemia is nearly universal in patients with cyanotic CHD, but clinical gout is relatively uncommon. Arthralgias, however, may be common. Hyperuricemia occurs as a result of increased production of uric acid and decreased renal clearance. Diuretics increase serum uric acid levels through hemoconcentration, decreased uric acid secretion, and increased reabsorption. Low fractional uric acid excretion is the primary mechanism of hyperuricemia in patients with cyanotic CHD.[212,213] Hyperuricemia is a marker of disease severity in cyanotic patients and is negatively correlated with cardiac index. Those with the highest uric acid levels had worse survival in a cohort of 94 patients with Eisenmenger syndrome.[214]

### Management

Hyperuricemia is diagnosed by testing serum uric acid, which should be done annually in cyanotic CHD.[2] Diagnosis of gout is difficult because patients with Eisenmenger syndrome often have pain resulting from hypertrophic osteoarthropathy and periostitis, which also cause bone pain and tenderness. Asymptomatic hyperuricemia does not require treatment. Colchicine can be used to treat gouty attacks, and xanthine oxidase inhibitors such as allopurinol or febuxostat can be used as prophylactic therapy in those with recurrent gout flares.

## Hemostasis

### Prevalence

Thrombosis is a common complication in adults with CHD; however, there are limited data on its prevalence. The majority of the literature has focused on the prevention and treatment of thrombosis in CHD in the pediatric population, including a scientific statement by the AHA.[215] Types of thrombotic complications associated with cyanosis are similar between pediatric and adult patients. However, adults with CHD are prone to arrhythmias, residual shunts, collaterals, and residual hemodynamic abnormalities that place them at increased risk for thromboembolic complications. Stroke incidence is higher in adults with CHD compared with the general population.[216]

Thromboembolic events contribute significantly to the morbidity and mortality of adults with Fontan

palliation.[217] Thrombosis occurs in 8% to 33% of patients with Fontan physiology, and incidentally discovered asymptomatic thrombosis is more common than clinically apparent thrombosis.[65,218–221] Thrombi can be seen in the venous pathway, the pulmonary arteries, the pulmonary venous atrium (particularly in the setting of atrial arrhythmias), or a ligated pulmonary artery stump. Thrombus is most commonly discovered in the first several years after surgery, and prevalence appears to diminish over time,[222,223] with a possible second peak in prevalence in later adulthood when hemodynamics deteriorate. Up to 7% of adult patients with Fontan physiology have a history of DVT, likely related to the high prevalence of chronic venous insufficiency in this population.[220]

### Pathogenesis

Eisenmenger syndrome patients are at simultaneous risk for thrombosis and hemorrhage. Unlike other forms of pulmonary arterial hypertension, Eisenmenger syndrome predisposes to bleeding resulting from alterations in platelet number, platelet function, and coagulation factors. Cyanotic patients often have a mild thrombocytopenia caused by ineffective thrombopoiesis and diminished platelet survival.[205,224,225] In addition, platelet dysfunction is reduced because of poor ADP-induced platelet aggregation.[226] Prothrombin time, partial thromboplastin time, and activated partial thromboplastin time are abnormal in ≈20% and are related to hepatic congestion, abnormalities in the vitamin K–dependent coagulation factors, and depletion of von Willebrand multimers.[111,227,228] In Eisenmenger syndrome, bleeding often presents as epistaxis, which is typically manageable, but can also present as hemoptysis, which can be catastrophic.[212,229]

A majority of patients with Fontan physiology have at least 1 abnormality in coagulation factors. After Fontan completion, factor VIII deficiency and protein C deficiency are the most common laboratory abnormalities (possibly predisposing to thrombosis), although alterations in nearly every coagulation factor have been described.[230,231] In addition, platelet activation and thrombin formation are enhanced and fibrinolysis is reduced, resulting in a prothrombotic state in most adult patients with Fontan physiology.[218] This is supported by the relatively high rate of thrombosis and the relatively low rates of clinical bleeding seen in adult patients with Fontan physiology. Defining coagulation abnormalities with standard laboratory testing is difficult; prothrombin time and partial thromboplastin time are often prolonged despite a procoagulant state. Testing of individual clotting factors is not routinely practiced.

Diagnosis of thromboembolism in patients with Fontan physiology poses a clinical challenge. D-dimer level may be a useful marker for systemic thromboembolism in patients with Fontan physiology.[232] DVT of the upper or lower extremity can be accurately diagnosed or excluded with compression ultrasound. Unfortunately, thrombus in the Fontan pathway and pulmonary thrombosis or embolism are much more difficult to diagnose. Because there is no subpulmonary mixing chamber in the Fontan to homogenize contrast, CT pulmonary angiograms with a standard protocol have significant swirling artifact, heterogeneous contrast enhancement, and a high rate of false-positive results.[233] Nuclear lung perfusion scans are similarly unreliable because of asymmetric pulmonary blood flow patterns. Multidetector CT angiography with simultaneous upper and lower extremity contrast power injection with early- and late-phase image acquisition can improve diagnostic accuracy.[234] Thrombus in the pulmonary venous atrium or intracardiac portion of the Fontan can be visualized by transesophageal echocardiography or alternatively CT or cardiac MR imaging.

Because of elevated hematocrit and decreased plasma volume in Eisenmenger syndrome, the use of standard laboratory testing leads to falsely prolonged prothrombin and activated partial thromboplastin times resulting from an inappropriate ratio between plasma and citrate anticoagulant. In patients with a hematocrit >55%, it is advisable that tubes with reduced sodium citrate be used to maintain a ratio of blood to anticoagulant of 9:1.[235–237] With appropriate citrate levels, laboratory testing includes platelet count, prothrombin time, and partial thromboplastin time.

### Management

Because of the ongoing risk of life-threatening bleeding and thrombosis in Eisenmenger syndrome, whether to anticoagulate this population is a therapeutic dilemma.[238] Anticoagulation appears to increase the rate of major bleeding; the rate of hemorrhage in Eisenmenger patients treated with anticoagulation was 16% in 1 study (compared with 0% in those not receiving anticoagulation), and fatal bleeding events were reported. Overall, the study did not show that anticoagulation affected survival.[239] Neither American nor European guidelines have made a recommendation for or against routine anticoagulation use in Eisenmenger syndrome, although many centers reserve its use for those with documented acute or chronic thrombosis.[2,240]

Given the high rate of thrombotic complications in patients with Fontan physiology, lifelong thromboprophylaxis is desirable, and a meta-analysis of nonrandomized data suggested that thromboprophylaxis reduced thrombotic complications.[241] There is no consensus as to whether antiplatelet therapy is adequate or therapeutic anticoagulation is needed in the absence of previous thromboembolism or arrhythmia, but limited data suggest equal efficacy of either strategy.[241,242] The relative safety and efficacy of non–vitamin K antagonist oral anticoagulants in adults with CHD have not been established, but multicenter trials are ongoing.

**Table 5. Genetic Syndromes With Cardiac Disorders and Associated Endocrinopathies**

| Syndrome | CHD Association | Endocrine Associations | Recommendations |
|---|---|---|---|
| Alagille | TOF, peripheral PS | Short stature<br>Osteoporosis | Tests: consider DEXA scan[246]<br>Treatment: calcium and vitamin D supplementation[246] |
| DiGeorge (22q11.2 deletion) | Conotruncal abnormalities (TOF, IAA, DORV), AVC, VSD, PDA, PS, vascular ring | Hypothyroidism (25%)<br>Hyperthyroidism (5%)<br>Hypoparathyroidism (80%)<br>Normal reproductive fitness | Tests: CBC, BMP, TSH, Ca, Mg, PTH, LFT, lipids, $HbA_{1c}$ annually[247]<br>Treatment: calcium and vitamin D supplementation[247] |
| Down | AVC, TOF, VSD, PDA | DM (3- to 10-fold increased risk)<br>Obesity<br>Hypothyroidism (up to 25%)<br>Hyperthyroidism (<5%)<br>Hyperlipidemia<br>Osteoporosis | Tests: lipids and TSH every 5 y; FPG/$HbA_{1c}$ every 3 y if >45 y of age or sooner if risk factors are present; DEXA scan every 2 y* or if any risk factors are present[14] |
| Kabuki | Coarctation of the aorta, ASD, VSD | Congenital hypothyroidism<br>Growth hormone deficiency | Tests: consider TSH[248] |
| Marfan | Dilated aortic root, mitral valve prolapse | Possible osteoporosis[249] | Tests: consider DEXA scan[249] |
| Noonan[250] | Pulmonic stenosis, hypertrophic cardiomyopathy | Delayed puberty<br>Reduced fertility in male patients<br>Short stature | Tests: no specific endocrine screening |
| Turner | Bicuspid aortic valve, CoA, dilated aorta | Hypogonadism<br>Hypothyroidism (24%)<br>Hyperthyroidism (2.5%)<br>Hyperlipidemia<br>Impaired glucose tolerance and DM (50%)<br>Osteopenia and osteoporosis<br>Short stature | Tests: DEXA scan every 3–5 y; TSH, LFTs, lipids, OGTT/$HbA_{1c}$ annually[251]<br>Treatment: discuss risk/benefit of estrogen replacement[251] |
| Williams-Beuren | Supravalvular aortic stenosis, supravalvular PS, peripheral PS, coronary artery abnormalities, midaortic syndrome, renal artery stenosis | Impaired glucose tolerance and DM (75%)<br>Osteopenia and osteoporosis (45%)<br>Subclinical hypothyroidism (15%–30%)<br>Hypercalcemia | Tests: BMP, Ca every 1–2 y; spot urine Ca/Cr ratio annually; TSH every 3 y; OGTT/$HbA_{1c}$ every 5 y; DEXA every 5 y[252,253]<br>Treatment: care with calcium supplementation given predisposition to hypercalcemia[252,253] |

AVC indicates atrioventricular canal; BMP, basic metabolic panel; CBC, complete blood count; CHD, congenital heart disease; CoA, coarctation of the aorta; Cr, creatinine; DEXA, dual-energy x-ray absorptiometry; DM, diabetes mellitus; DORV, double-outlet right ventricle; FPG, fasting plasma glucose; $HbA_{1c}$, hemoglobin $A_{1c}$; IAA, interrupted aortic arch; LFT, liver function test; OGTT, oral glucose tolerance test; PDA, patent ductus arteriosus; PS, pulmonic stenosis; PTH, parathyroid hormone; TOF, tetralogy of Fallot; TSH, thyroid-stimulating hormone; and VSD, ventricular septal defect.

*Adults with Down syndrome ≥40 years of age living in institutions and ≥45 years of age living in the community.





## ENDOCRINE

Endocrinopathies are often associated with specific syndromes in patients with CHD. For example, thyroid disorders and DM are frequently encountered in Down, Turner, and Williams-Beuren syndromes. DiGeorge syndrome (22q11.2 deletion syndrome) is associated with hypocalcemia and thyroid disease. However, disorders of calcium metabolism are not isolated to patients with genetic syndromes. Patients with Fontan physiology and patients with advanced heart failure are especially at risk for low vitamin D, elevated parathyroid hormone, and abnormal bone density.[243,244] As adults with CHD age, they may develop cardiovascular risk factors for atherosclerotic disease such as obesity, DM, hyperlipidemia, and metabolic syndrome. It is essential for the ACHD practitioner to partner with an endocrinologist familiar with CHD-related endocrinopathies and metabolic disorders.

### Thyroid

#### *Prevalence and Pathogenesis*

Hypothyroidism, which affects almost 10% of the ACHD population, is one of the most common endocrine abnormalities in CHD.[245] It is particularly associated with cyanosis, genetic syndromes (particularly Down syndrome), and the use of amiodarone (Table 5). The prevalence of hypothyroidism in children and adults with Down syndrome has been reported to be as high as 4% to 18%.[254–256] The incidence increases over time and may relate to inadequate thyroid tissue or the increased incidence of autoimmunity in Down syndrome.[257] Adults with TOF and syndromic features have an elevated prev-

alence of thyroid dysfunction (20%), similar to those with 22q11.2 deletion at 21% to 25%,[247,258] which may be related to abnormal thyroid development from neural crest cells. The incidence of hypothyroidism in Turner syndrome is 24% to 31%.[251,259] In adults with CHD taking amiodarone, the incidence of hypothyroidism is 12% to 15%.[260,261] Amiodarone-induced hyperthyroidism occurs in 14% to 21% of treated patients with ACHD,[260–262] which is higher than the 2% to 10% incidence in unselected populations.[263–265] Risk factors for amiodarone-induced hyperthyroidism in CHD include female sex, low body mass index (BMI), complex cyanotic CHD, Fontan palliation, lower age, goiter, heart failure, and dose >200 mg/d.[260,261,266] There is a small but important incidence of thyrotoxicosis in patients receiving prostacyclin therapy for pulmonary hypertension, and this is a consideration in an otherwise stable patient presenting with acute decompensation on this therapy.[267] Abnormal autoimmunity accounts for increased rates of hyperthyroidism in Down, Turner, and 22q11.2 deletion syndromes (Table 5).

### *Diagnosis/Management*

There is controversy about routine thyroid screening in the asymptomatic general population.[268] The American Association of Clinical Endocrinologists recommends that screening be considered in patients at risk for thyroid disorders.[268] Therefore, one can consider routine thyroid screening in adults with CHD who have a higher prevalence of thyroid disorders such as patients with Down syndrome. Guidelines by the Heart Rhythm Society recommend testing of thyroid-stimulating hormone and free thyroxine every 6 months or sooner on the basis of clinical symptoms in patients receiving amiodarone.[80,269] The management of thyroid dysfunction in medically complicated individuals occurs in collaboration with an endocrinologist. Overall management of hypothyroidism is not different in the adult with CHD, although several important issues are noted. The incidence of atrial arrhythmias is significantly increased in the adult patient with CHD[270]; therefore, gradual uptitration of thyroid replacement is warranted. Thyroid dysfunction is a risk factor for poor outcome in patients with ACHD undergoing cardiac surgery and should be carefully assessed before surgery.[19] Amiodarone-induced thyrotoxicosis is treated as it would be in the general population. Given the high mortality associated with intravenous prostaglandin-associated hyperthyroidism, treatment as an inpatient or in the intensive care unit is advised.

## Calcium Hemostasis and Bone Health

### *Prevalence and Pathogenesis*

Disordered bone, calcium, and vitamin D metabolism may lead to increased rates of bone disease and predispose to fractures. Particular at-risk populations include patients with a single ventricle with Fontan palliation (especially with a history of PLE) and patients with advanced heart failure or cyanosis.[243] Those suffering from PLE or treated with corticosteroids appear to be at highest risk.[271] Low vitamin D and elevated parathyroid hormone levels appear to be associated with CHD.[272–274] It is well established that adults with advanced heart failure have lower bone mass and vitamin D levels,[244] with approximately half of patients with severe heart failure having osteopenia or osteoporosis, so it is of concern that a significant number of patients with complex CHD at such a young age have demonstrated markers of abnormal bone density/function because this may be a harbinger of osteopenia, osteoporosis, and fracture risk later in life. Patients with Down syndrome are at increased risk for low bone mineral density and fractures.[275] Turner syndrome is associated with increased risk of osteoporosis, linked to estrogen deficiency (Table 5). Patients with 22q11.2 deletion syndrome can have hypoparathyroidism, resulting in hypocalcemia and tetany, which occurs in infancy but can occur at any time throughout the life span, with ≈80% experiencing this at some point.[276] Hypocalcemia can cause seizures and arrhythmias.

The causes of low bone mineral density, low vitamin D, and elevated parathyroid hormone in Fontan, cyanotic, advanced heart failure, and Down/Turner syndrome patients are myriad. Hypoxemia, reduced activity, reduced sunlight exposure, use of long-term corticosteroids for treatment of PLE, and abnormal diet all may contribute.

### *Diagnosis/Management*

Population-based screening remains controversial for the detection of osteoporosis. The Association of Clinical Endocrinologists recommends screening all women ≥65 years of age, younger perimenopausal or postmenopausal women with clinical risk factors for fracture, and any adult with a history of fracture not caused by severe trauma.[277] Further study is needed in adults with CHD of bone density and vitamin D deficiency. Many clinical risk factors for fracture, including advanced age, reduced physical activity, malabsorption, glucocorticoid therapy, and secondary osteoporosis from chronic liver disease, may be applicable to patients with CHD with Fontan palliation or advanced heart failure. It is reasonable to follow guideline-based screening with dual-energy x-ray absorptiometry in adults with CHD. Assessment of serum calcium, vitamin D, and possibly parathyroid hormone concentration can be considered in adults with CHD.

Management includes calcium supplementation, vitamin D supplementation, an exercise plan that includes weight-bearing exercise, and regular monitoring by and review with an endocrinologist. The use of antiresorptive therapy has not been well studied in this group of patients. A high index of suspicion for frac-







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tures is maintained because this may provide a clue to underlying bone pathology.

## Obesity and Metabolic Syndrome

### *Prevalence and Pathogenesis*

Currently, it is estimated that 69% of US adults are at least overweight (BMI, 25–29.9 kg/m$^2$) and ≈35% are obese (BMI ≥30 kg/m$^2$).[278] Of great concern to the physician caring for adults with CHD is the increased cardiovascular morbidity and mortality associated with obesity and the metabolic syndrome superimposed on the sequelae of CHD.[279]

The prevalence of obesity in adults with CHD appears to be comparable to that of the general population, with an estimated prevalence of 40% to 54%.[280,281] In those undergoing redo cardiac surgery, obesity was present in 30%.[282] In terms of specific CHD lesions, data from several cohorts suggest a high rate of overweight and obesity in patients with Fontan physiology in the United States at 30% to 39%,[283–285] associated with pre-Fontan weight and Hispanic ethnicity. These findings mirror documented rates of overweight and obesity in children with various forms of CHD in the United States at 26% to 30%.[286–288]

Rates of metabolic syndrome are higher in adults with CHD compared with the general population. In a cohort-based study in the United States, metabolic syndrome was present in 15% of adults with CHD versus 7% in controls.[289] This finding was driven by a much higher prevalence of hypertriglyceridemia, low high-density lipoprotein, and fasting hyperglycemia in the adults with CHD. A Korean study showed a similarly higher rate of metabolic syndrome in the surgically corrected ACHD group of 37% versus 24% in control subjects.[290] Cyanotic CHD was protective against metabolic syndrome in this cohort.

The causes of overweight/obesity and metabolic syndrome are likely multifactorial. Adults with CHD may be more sedentary because of restrictions placed by physicians leading to deconditioning or by intrinsic physical limitations related to underlying defects.[291] It is postulated that abnormal growth patterns during childhood, characterized by initial low body mass followed by a rapid "catch-up" growth phase after palliation and subsequent emphasis on weight gain on the part of both families and providers, may lead to an increased risk of atherosclerotic cardiovascular disease later in life.[292,293]

As in the rest of the population, obesity appears to exert a negative impact on outcomes in adults with CHD. Postoperative complications with longer length of stay and postoperative arrhythmias have been reported in obese patients with CHD undergoing pulmonary valve replacement.[294] The untoward effects of increased afterload on ventricular function are of particular significance for those with systemic right or single ventricles. Of concern is the correlation between obesity and symptomatic heart failure, accelerated liver disease, and mortality in adult patients with Fontan physiology.[295]

**Table 6. Screening for Atherosclerotic Cardiovascular Risk Factors in Adults With CHD**

| | Testing | Frequency |
|---|---|---|
| Diet and physical activity | NA | Yearly[296] |
| Tobacco | NA | Yearly[296] |
| Hypertension | Office blood pressure measurement and/or ambulatory/home blood pressure monitor | Yearly[297] |
| Obesity | Weight, height, and BMI | Yearly[298] |
| Dyslipidemia | Fasting lipid panel | Every 5 y[299] |
| DM | Fasting plasma glucose, oral glucose tolerance test, or hemoglobin $A_{1c}$ | Every 3 y in adults ≥45 y of age or ≤45 y of age with BMI ≥25 kg/m$^2$ and risk factors for DM[300] |
| PAD | Ankle-brachial index | Insufficient evidence but can consider in patients with DM or an additional cardiovascular risk factor[301] |

BMI indicates body mass index; CHD, congenital heart disease; DM, diabetes mellitus; NA, not available; and PAD, peripheral artery disease.



### *Management*

Routine assessment of weight, BMI, and waist circumference on a yearly basis is appropriate (Table 6).[298] Management of obesity involves a comprehensive discussion and plan for calorie restriction, intense face-to-face or over-the-phone counseling, physical activity, and long-term maintenance.[298] Referral to a nutrition professional for counseling is likely to be beneficial. Bariatric surgery for the treatment of obesity may be appropriate in individuals with a BMI ≥40 kg/m$^2$ or ≥35 kg/m$^2$ with obesity-related comorbid conditions.[298] Further consultation with a bariatric surgeon may be beneficial with consideration for the risk for perioperative and postoperative hypoxia. Management of the metabolic syndrome includes recommendations for exercise, lifestyle modification, and management of its individual components of obesity, insulin resistance, hypertension, and dyslipidemia.

## Diabetes Mellitus

### *Prevalence and Pathogenesis*

DM prevalence rates in the general US population have increased from 3.5% in 1980 to a current estimate of

9%.[302] Data from several studies suggest that there is an increased risk for DM in adults with CHD. A single-center study showed rates of fasting hyperglycemia of 40% in adults with CHD versus 9% in matched controls.[289] A population-based study from Denmark showed new onset of DM in 4% between 30 and 45 years of age with a hazard ratio of 1.35 of new DM in adults with CHD compared with the general population.[303] This study noted that this risk was concentrated in individuals with repaired cyanotic CHD (hazard ratio, 2.85), although the reasons remain unclear. Impaired glucose tolerance and prediabetes have been demonstrated in almost 40% of adults with CHD.[304,305] Patients with Down, Turner, and Williams-Beuren syndromes have markedly increased risk of DM (Table 5). The causes of these important differences from the general population are hard to determine from available data but may relate to increased rates of obesity and reduced physical exercise. The impact of DM on patients with CHD has been suggested to increase morbidity and mortality compared with diabetic individuals without CHD.[306]

### *Diagnosis/Management*

The diagnosis and management of DM are beyond the scope of this review. Screening for DM with fasting plasma glucose, oral glucose tolerance test, or hemoglobin $A_{1c}$ is recommended at 3-year intervals by the American Diabetes Association in adults ≥45 years of age or in those <45 years of age who have a BMI ≥25 kg/m$^2$ and an additional risk factor for DM (Table 6).[300] In adults with CHD, DM screening has been recommended in all those ≥40 years of age with a BMI ≥25 kg/m$^2$ with or without risk factors.[307] Physician emphasis on healthy weight, diet, and increased exercise is an important part of management. There are no specific limitations on standard dietary and medical therapy for adults with concomitant DM and CHD, and usual goals for reducing hemoglobin $A_{1c}$ are pursued. It is appropriate to consider the degree of reactive erythrocytosis and the hemoglobin concentration in the interpretation of hemoglobin $A_{1c}$ in cyanotic patients, and in this situation, afructosamine level may be useful.

## Lipid Abnormalities

### *Prevalence and Pathogenesis*

Dyslipidemia has been studied in several cohorts of adults with CHD, with estimates ranging from 27% to 60% with abnormal lipid levels.[4,289,305,307] Lipoprotein(a) levels were found to be similar to those in the general cohort.[308] A Korean study found low-density lipoprotein to be higher and high-density lipoprotein lower in patients with CHD than in a control group.[290] Low high-density lipoprotein and high triglycerides may be related to the same factors promoting metabolic syndrome in these patients.[289] Although data remain limited to single centers or administrative databases, the prevalence of dyslipidemia appears to be similar to that in the general population.[307]

### *Diagnosis/Management*

The diagnosis and management of hyperlipidemia are well established in the general population and are reviewed elsewhere.[299,309] Certain CHD populations such as those with CoA or transposition of the great arteries after arterial switch operation may be at increased atherosclerotic cardiovascular risk and warrant aggressive risk factor modification.[307] The role of conventional medical therapy is not well established in ACHD, although atorvastatin and ramipril were found to lower serum markers of vascular inflammation in a cohort of normotensive patients with CoA, in whom these markers are known to be abnormal.[310,311]

# ONCOLOGY

## Prevalence

Cancer is the fourth leading cause of mortality after heart failure, pneumonia, and sudden cardiac death in a large registry of adults with CHD, with an increasing proportion of death resulting from noncardiac causes with older age.[16] Indeed, cancer was a predictor of all-cause mortality in an analysis of adult patients with CHD >65 years of age,[4] highlighting the need to address age-related noncardiac morbidities such as malignancy in this population.

The prevalence of cancer in adults with CHD in Quebec is 1.6 to 2 times higher than that in the general Canadian population.[312] A population-based study from Taiwan of 31 961 individuals with a CHD diagnosis identified from a national database showed an increased risk of cancer compared with the general population (standardized incidence ratio, 1.45; 95% confidence interval, 1.25–1.67).[313] Death caused by cancer is higher in adults with CHD. A large study of 10 964 patients who underwent pediatric cardiac surgery in Finland between 1953 and 2009 with up to 60 years of follow-up demonstrated that death caused by neoplasm was more common in patients with CHD compared with the general population, particularly among female patients who underwent surgery between 1990 and 2009.[15]

## Pathogenesis

The use of low-dose ionizing radiation from medical diagnostics and procedures is a risk factor for carcinogenesis, and its use in the management of CHD has increased steadily over time. In a population-based study in Quebec of children and adults with CHD, the number of cardiac procedures associated with low-dose ionizing







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radiation increased from 18.5 to 51.9 per 1000 patients with CHD per year from 1990 to 2005 ($P<0.0001$), driven primarily by a growing number of diagnostic catheterizations.[314] Age at the time of first exposure of radiation in children decreased from 5 years to 9.6 months during the study period, reflecting increasing accessibility and general acceptance of these types of procedures as standard of care.[314]

## Genetic Causes

A risk factor for CHD and malignancy may be shared genetic linkage. There is a strong association between congenital malformations and cancer that is particularly well established in Down syndrome.[315–318] In an analysis of 15 905 patients with CHD from a Danish national registry followed up to 31 years, the observed increase in the overall risk of cancer compared with the general population was driven by individuals with Down syndrome.[319]

Other syndromes associated with congenital anomalies and increased cancer risk include Noonan syndrome, Fanconi anemia, and 22q11.2 deletion syndrome. Germline gene mutation of protein tyrosine phosphatase nonreceptor type 11 gene (*PTPN11*) in Noonan syndrome and other genetic disorders of the renin-angiotensin system–mitogen-activated protein kinase signaling pathway (RASopathies) has been linked to leukemia and solid tumors.[320–322] Fanconi anemia is an autosomal and X-linked recessive condition characterized by bone marrow failure and high risk of leukemia and solid tumors with multisystem involvement, including CHD (ventricular septal defect, patent ductus arteriosus, pulmonic or aortic valve stenosis, CoA and arch anomalies, TOF) in 6% to 10%.[323,324] The deletion of 22q11.2 is a common genetic syndrome associated with conotruncal CHD that also may form the basis for tumorigenesis.[325,326]

Teratogenesis and carcinogenesis may share a common basis for some cancer sites,[318] and putative mechanisms include point mutations in specific genes that may lead to both cancer and congenital anomalies or mutations in a developmental gene early in embryogenesis.[316] However, children born with congenital defects are at higher risk for cancer early in life,[327] and the mechanism for childhood malignancy in these cases may be distinct from malignancy diagnosed later in adulthood.[316]

## Low-Dose Ionizing Radiation and Malignancy in CHD

The vast majority of research on oncological issues and CHD has focused on radiation exposure, especially that sustained in childhood, which may play a significant role in later-onset malignancy. The BEIR (Biological Effects of Ionizing Radiation) VII report from the National Research Council of the National Academies advocates a linear no-threshold hypothesis that states that there is no threshold below which radiation cannot cause malignancy and describes a linear increase of malignancy with radiation dose.[328] Low-dose ionizing radiation for medical use is acknowledged as a risk factor for the development of cancer.[329–331] Specifically, a positive correlation between exposure to low-dose ionizing radiation and incidence cancer risk has been demonstrated in adults with CHD.[332]

Age at the time of radiation exposure is a critical determinant of cancer risk. Adults with CHD have often been exposed to studies using radiation in childhood. Historically, cardiac catheterization was the primary modality for CHD diagnosis before the advent of echocardiography in the 1980s. Children have been estimated to have a higher risk of cancer compared with adults because they have more rapidly dividing cells, more closely spaced organs leading to radiation outside the area of interest, and longer life expectancy.[328,333]

Cardiac catheterization and CT scans account for the majority of radiation in the management of CHD, specifically 81% to 95% in contemporary pediatric cardiology practice.[333,334] In a cohort of 337 children ≤6 years of age who had undergone cardiac surgery, cardiac catheterizations represented 1.5% of all testing associated with radiation but accounted for 60% of the total radiation exposure. Populations at risk for more exposure to low-dose ionizing radiation procedures and repetitive imaging are children, especially those with complex CHD, and those with genetic syndromes.[314,335,336] Johnson et al[334] demonstrated a wide range of radiation exposure depending on CHD complexity: 0.19 mSv (95% confidence interval, 0.07–29.28) for atrial septal defect repair compared with 28.93 mSv (95% confidence interval, 0.08–76.93) for those who underwent the Norwood operation. The lifetime exposure for an adolescent with CHD is estimated to be ≈20 mSv.[337]

The data on long-term outcomes on incidence of and mortality from cancer in patients with CHD exposed to ionizing radiation in childhood are mixed.[338–340] To adequately quantify risk from doses of radiation ≤10 mSv, decades of follow-up in millions of people would be required because of the low incidence of cancer.[341] To address these epidemiological limitations, other surrogate markers for carcinogenic end point have been examined. Both short- and long-term damage in the form of circulating lymphocytes as biomarkers of genetic damage from cardiac catheterization has been shown.[333,342] Adolescents who were exposed to ionizing radiation at <1 year of age had up to a 3-fold increase in chromosomal aberration in circulating lymphocytes years after exposure.[337] An excess number of γ-H2AX foci (a marker of breaks in double-stranded DNA that is considered one of the most dangerous chromosomal alterations

from exposure to ionizing radiation) have been shown to occur after pediatric cardiac catheterization.[343]

Solid cancer incidence in atomic bomb survivors varies by sex, age at exposure, and attained age.[344] The BEIR VII report estimates that the lifetime attributable risk (LAR) of cancer incidence associated with a single cardiac catheterization is 2.1% (1 in 476) in female patients and 0.8% (1 in 1250) in male patients.[345] In a recent study, organ-specific radiation dose from a variety of catheterization procedures in children ranged from an LAR of <1 in 2000 for atrial septal defect closure to 1 in 150 for transcatheter valve replacements.[346] Of particular importance was the strong modification of LAR cancer incidence depending on survival, with a lower LAR incidence by 7-fold for those with a life expectancy of 50 years. Women are at particular risk, and breast cancer is of particular concern especially after transcatheter valve replacement.[346]

## Special Populations

There are increasingly more reports of HCC in patients with Fontan physiology in the literature.[119,127,347–349] The liver in the Fontan circulation is at risk for FALD (see Liver), which is characterized by congestion, fibrosis, and cirrhosis, which ultimately places these patients at risk for HCC.[120] In addition to being subjected to the physiological alterations characteristic of Fontan physiology (increased central venous pressure and low cardiac output), the liver in the patient with a single ventricle is vulnerable to a number of insults to the liver that begin well before Fontan completion (hypoxia, low output state, and perioperative insult).[350,351]

Neuroendocrine tumors such as pheochromocytoma and paraganglioma have been documented in the setting of cyanotic CHD going back to the 1960s.[352–355] Chronic hypoxia was hypothesized to be the trigger on the basis of observations of a higher incidence in high-altitude dwellers.[356] A number of genes have been identified that are associated with these neoplasms, including mitochondrial succinate dehydrogenase (SDH) complex subunits A, SDHB, SDHC, SDHD, and SDH5 and Von Hippel Lindau tumor suppressor genes.[357] More recently, there is evidence supporting a putative molecular mechanism linking hypoxia and neuroendocrine tumorigenesis, or the (pseudo) hypoxia hypothesis.[358,359] SDH and Von Hippel Lindau gene mutations lead to dysregulation of hypoxia-inducible genes, activating a pathway of chronic hypoxic stimulation, which results in cellular proliferation, angiogenesis, apoptosis, and metastasis.[359]

## Management

Radiation-induced solid cancers tend to occur at ages at which they are normally diagnosed in the general population.[344] Although radiation-induced leukemia manifests within 3 to 5 years after radiation exposure, solid tumors generally appear at least 10 to 15 years after exposure and often are not diagnosed until adulthood.[360] The most common types of cancer in adults with CHD mirror those of the general population: breast, colorectal, and uterine for women and prostate, colorectal, and bladder for men.[312] For these reasons, age-appropriate cancer screening for adults with CHD is recommended (Table 7).

In addition to age-appropriate cancer screening, certain types of cancers associated with medical radiation are worth mentioning given the proximity of these organs to the heart. Specific organs that are particularly radiosensitive in children are thyroid, breast, bone marrow, brain, and skin.[360] Thyroid cancer is particularly sensitive to radiation, and a linear dose-response relationship has been demonstrated, with younger age at exposure and female patients at particular risk.[371] Breast cancer risk is also linearly related to dose and age at exposure, with this risk persisting up to 50 years after radiation exposure.[372,373]

Patients should be educated on low-dose ionizing radiation associated with medical studies and procedures. Risks of not performing cardiac studies that involve low-dose ionizing radiation are weighed against a small risk of inducing malignancy, and patients ought to be involved in the decision-making process. This conversation is more challenging with a younger population such as adult CHD survivors because radiation-induced malignancies have a biological latency of ≈10 to 40 years.[374] The LAR of cancer incidence is higher with younger age at exposure according to models of cancer risk outlined in the BEIR VII report.[328] Life expectancy is a strong modifier of cancer risk and taken into account in these discussions.[346]

There are no practice guidelines on the surveillance of HCC in patients with Fontan physiology. Table 2 summarizes recommendations for surveillance of FALD. The American Association for the Study of Liver Diseases practice guideline for the management of HCC does not address cardiac cirrhosis or FALD.[134] The guideline does suggest that it is cost-effective to screen for HCC if the risk exceeds 1.5%/y in patients with hepatitis C.[134] An incidence of 1.5%/y to 5%/y for HCC has been suggested in patients with Fontan physiology.[127] Therefore, guideline-based screening for HCC may be reasonable in FALD, which in cirrhotic patients is based largely on ultrasound examination. CT or MR imaging may be recommended at the discretion of the hepatologist or if a liver nodule >1 cm is identified. The role of AFP remains controversial. The American Association for the Study of Liver Diseases no longer recommends the use of AFP as a screening tool,[134] but AFP in conjunction with imaging may improve the specificity for HCC in patients with Fontan physiology. Management of HCC is not well defined in FALD but may include transarterial chemoembolization, percutaneous ablation, surgical resection, and liver transplantation.[134]

**Table 7. Recommendations for Cancer Screening**

| | USPSTF | ACS |
|---|---|---|
| Breast | Women* 50–74 y of age: biennial screening mammography is recommended.<br>Women* 40–49 y of age: individual decision but women with parent, sibling, or child with breast cancer are at higher risk and may benefit from earlier screening.[361] | Women with average risk who are 45–54 y of age: annual screening mammography.<br>Women with average risk who are ≥55 y of age: biennial screening mammography or the opportunity to continue annual screening.<br>Women should have the opportunity to be screened annually between 40 and 44 y of age.<br>Women should continue screening mammography as long as their health is overall good and life expectancy at least 10 y.<br>Clinical breast examination among average-risk women is not recommended.[362] |
| Colorectal | Adults 50–75 y of age: screening is recommended by stool-based tests or direct visualization with frequency depending on method.<br>Adults 76–85 y of age: individual decision taking into account overall health and screening history.[363] | ACS/US Multisociety Task Force on Colorectal Cancer/American College of Radiology 2008 guidelines recommend that clinicians help patients choose between stool-based test and direct visualization and emphasize prevention rather than screening.[364]<br>Adults ≥50 y of age with average risk: consider flexible sigmoidoscopy every 5 y, colonoscopy every 10 y, double-contrast barium enema every 5 y, CT colonography every 5 y or guaiac-based fecal occult blood test every 5 y, fecal immunochemical test every year, stool DNA test every 3 y. |
| Prostate | Recommendation against PSA-based screening.[365] | Individual decision to screen. For those who decide to be screened, PSA testing with or without DRE for average-risk men beginning at 50 y of age. Screening discussion may begin at 40–45 y of age for high-risk population (blacks and those with first-degree relative with prostate cancer before 65 y of age).[366] |
| Lung | Adults 55–80 y of age: annual screening is recommended with LDCT for those who have 30–pack-y history and currently smoke or have quit within past 15 y.[367] | Adults 55–74 y of age: annual screening is recommended with LDCT for those who have 30–pack-y history of smoking and currently smoke or have quit within past 15 y or 50 y of age with cumulative risk >5% over next 5 y.[368] |
| Cervical | Women† 21–65 y of age: Pap smear every 3 y<br>Women† 30–65 y of age: Pap smear and screening for HPV every 5 y[369] | ACS/American Society for Colposcopy and Cervical Pathology/ American Society for Clinical Pathology 2012 guidelines recommend Pap smear every 3 y for women 21–29 y of age and Pap smear plus screening for HPV every 5 y for women 30–65 y of age.[370] |

ACS indicates American Cancer Society; CT, computed tomography; DRE, digital rectal examination; HPV, human papilloma virus; LDCT, low-dose computed tomography; PSA, prostate-specific antigen; and USPSTF, US Preventive Services Task Force.

*These recommendations apply to asymptomatic women ≥40 years of age who do not have preexisting breast cancer or a previously diagnosed high-risk breast lesion and who are not at high risk for breast cancer because of a known underlying genetic mutation (such as a *BRCA1* or *BRCA2* gene mutation or other familial breast cancer syndrome) or a history of chest radiation at a young age.

†This recommendation statement applies to women who have a cervix, regardless of sexual history. This recommendation statement does not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive).





# VASCULAR

Vascular disease is made up of a heterogeneous set of disorders that may accompany CHD in adulthood. Both arterial and venous vasculature can be affected with involvement of systemic and pulmonary circulations, including aortic, cerebral, and peripheral vascular beds. Pathogenetic factors include genetic syndromes, anatomic malformations, previous vascular interventions, and various physiological disturbances.

## Cerebrovascular Disease

### *Prevalence and Pathogenesis*

The risk of cerebrovascular disease, including stroke and transient ischemic attacks, exists across myriad ACHD diagnoses.[216] Among adults with CHD, 1 in 11 men and 1 in 15 women experience a stroke between 18 and 64 years of age.[216] Stroke incidence is higher than in the general population, especially at a younger age. The cumulative risk of ischemic stroke is higher than that of hemorrhagic stroke in this population. Individuals with heart failure, DM, and recent myocardial infarction may be at greatest risk for ischemic stroke.[216]

The pathogenesis of cerebrovascular disease among adults with CHD may relate to inherent coagulation abnormalities such as in patients with a single ventricle [110] but may also relate to structural arterial findings in CoA or other CHD associated with vascular arteriopathy.[375] Embolic phenomenon must be considered in the ACHD population, especially in individuals with mechanical valves, right-to-left shunt lesions, and atrial arrhythmias, particularly in the presence of depressed ventricular function or akinetic segments.[376]

Atrial arrhythmias delineate a subset of individuals with increased risk of thromboembolism in adults with CHD. Nearly 75% of individuals with an atriopulmonary Fontan and atrial fibrillation or flutter have intracardiac

thrombi, with lower, although still concerning, rates of thrombus formation (≈10%–15%) in those with lateral tunnel or right atrium to right ventricular outflow tract connections.[377] Nearly 16% of these patients had documented stroke, and 5% of patients had PEs during follow-up, although fortunately the risk of thromboembolism associated with cardioversion in the setting of anticoagulation is very low.

Subarachnoid hemorrhage from ruptured intracranial aneurysm is a rare but devastating phenomenon in ACHD. Studies have suggested that adults with CoA have a 5-fold higher prevalence of intracranial aneurysms (≈10% versus ≈2%), occurring at an earlier age, than in the general population.[378] Diagnosis is more common at an older age in the CoA population (median age of individuals with aneurysm versus without aneurysm, 37 versus 23 years).[379] Individuals with CoA and hypertension appear to have a 2-fold higher incidence of intracranial aneurysm, suggesting increased hypertension with age or perhaps a pathophysiological factor influencing aneurysm formation, although much more data are needed to assess correlation.[379] More recent studies suggest that in children treated early for CoA, there is no clear association of CoA and intracranial aneurysm, but they perhaps still support the possibility that hypertension may contribute to aneurysm development in adults with CoA.[379,380]

### *Management*

Atrial arrhythmias are common in ACHD, and there is a high incidence of stroke in those with atrial fibrillation. In those groups with a higher incidence of atrial fibrillation, rhythm monitoring, often longer term, at regular intervals is essential for diagnosing asymptomatic atrial fibrillation in order to recommend rhythm management when indicated and anticoagulation, considering the high risk of thromboembolism. One recent study revealed that the mean pre-event $CHA_2DS_2$-VASc (Congestive Heart Failure, Hypertension, Age, Diabetes, Previous Stroke/Transient Ischemic Attack and Vascular Disease) score was 1 in an at-risk ACHD population with atrial fibrillation, suggesting that this scoring system may underperform in stroke risk stratification in adults with CHD.[376] Another retrospective multicenter cohort study of patients with CHD with documented sustained atrial arrhythmias revealed that antiplatelet therapy was administered to 38%, anticoagulation to 54%, and neither to 8% with 85% freedom from thromboembolic events at 15 years and no difference between anticoagulation and antiplatelet therapy.[381] Thromboembolic events were predicted by disease complexity but not by $CHADS_2$/$CHA_2DS_2$-VASc scores, and the HAS-BLED (Hypertension, Abnormal Renal and Liver Function, Stroke, Bleeding, Labile INR, Elderly, Drugs or Alcohol) score was useful in predicting major bleeds.[381]

In addition to anticoagulation in individuals with atrial arrhythmia and cerebrovascular accident risk, individuals with right-to-left intracardiac shunts have a high stroke rate, so anticoagulation as part of the management algorithm should be discussed with an ACHD multidisciplinary team. Paradoxical embolic events are also common in adults with Ebstein anomaly with severe tricuspid regurgitation and are strongly associated with atrial septal defect. In patients with Ebstein anomaly and atrial septal defect or patent foramen ovale, shunt closure can be considered to reduce the risk of possible paradoxical embolic events if physiology allows.[382] The patient with a fenestration in the Fontan pathway is also at risk for paradoxical embolism. Cerebrovascular imaging with both MR and CT offers unique information and is undertaken in collaboration with neurology or neuroradiology for optimal data collection. Further research is needed to consider screening with MR angiography for vasculopathy in adults with CHD.[379,380]

## Peripheral Venous and Arterial Disease

### *Prevalence and Pathogenesis*

Venous insufficiency presents primarily in the Fontan circulation but also in other elevated right-sided heart pressure states. The prevalence of venous reflux is 5-fold higher in patients with Fontan physiology compared with healthy control subjects and does not correlate with clinical venous insufficiency (only half of patients with Fontan physiology with observed venous reflux demonstrate clinical signs of venous disease).[383] Individuals with a single right ventricle, those dependent on antiarrhythmic medications, and those with a family history of venous disease are at highest risk of documented venous insufficiency.[383] The medial malleolar area, as with chronic venous insufficiency in any individual, should be clinically assessed for CEAP (clinical, etiological, anatomic, pathophysiological) class V and VI ulceration because it may provide a source for bacteremia in this population. Patients with previous venous intervention such as right-sided heart cardiac hemodynamic catheterizations and in some cases femoral vein ligation may be at particular risk for chronic venous insufficiency.[220]

Unfortunately, DVTs and PEs are less well-defined but common vascular disease associations seen in adults with CHD. There is an increased risk of DVT in patients with interrupted inferior vena cava; therefore, the left isomerism or polysplenia syndrome requires that particular attention be paid to DVT risk assessment.[384] Vascular access challenges from early and multiple procedures, including recurrent catheterizations and sometimes cut-downs for improved access to the vasculature in a child, must be assessed in any adult with repaired CHD.







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Peripheral artery disease (PAD) may occur with age in the ACHD population in correlation with classic atherosclerotic risk factors (tobacco use, dyslipidemia, DM) and may coexist with coronary artery disease, atrial fibrillation, cerebrovascular disease, and renal disease. Therefore, in an adult with CHD and PAD, assessment of these associated conditions is essential. Unique to the ACHD population, individuals with recurrent childhood arterial access for cardiovascular assessment, especially the CoA population, may be at higher risk of focal arterial stenoses. Additional contributors to PAD in the adult with CHD can include hyperviscosity, phlebitis, previous surgery or cannulation site, and coagulopathy. PAD is generally chronic in presentation. If acute symptoms occur, imaging and assessment of causes for embolic events leading to acute limb ischemia must be done rapidly. Although less common, vascular infection ought to be considered in the immediate postprocedural setting and as a contributor to peripheral vascular disease but is generally accompanied by classic infectious presentation. In the aging ACHD population, atrial fibrillation, valvular disease, recent myocardial infarction, and artherosclerotic disease may all contribute to increasing rates of PAD in the next decade.

### *Diagnosis and Management*

Lower extremity ultrasound is the diagnostic modality of choice for the assessment of venous insufficiency and venous thromboembolism. Dedicated lower extremity muscle training and venous compression stockings may benefit patients with chronic venous insufficiency.[220] CT angiographic evaluation for PE may be difficult to perform and interpret, especially when there is an abnormal pulmonary flow pattern, and is best performed in a regional ACHD center. Noninvasive testing such as pulse wave velocity and ankle-brachial index can be diagnostic (Table 6), in addition to classic PAD presentation, including intermittent claudication with symptoms precipitated by walking and relieved at rest. However, the development of collateral circulation over time may reduce recognizable symptoms; therefore, exercise ankle-brachial index assessment is useful in adults with coarctation to uncover asymptomatic decreased lower extremity perfusion.

## Aortopathy

### *Prevalence and Pathogenesis*

Dilatation of the aortic root and the ascending aorta is frequently encountered in adults with CHD. Aortic dilation associated with CoA, bicuspid aortic valve, and genetic syndromes with connective tissue disorders such as Marfan, Loeys-Dietz, vascular Ehlers-Danlos, and Turner syndromes is generally well recognized and is not addressed here. However, primary aortic dilation also is seen in association with conotruncal abnormalities such as TOF, pulmonary atresia with ventricular septal defect, double-outlet right ventricle, or truncus arteriosus. Genetic predisposition, hemodynamic effects, and intrinsic arterial wall abnormalities (fibrosis, elastic fiber fragmentation, cystic medial necrosis) likely together contribute to aortic dilation in the conotruncal population.[385,386] A right-sided aortic arch, male sex, history of an aortopulmonary shunt, and complete repair at older age have been associated with late aortic dilatation.[387] Aortic dissection late after TOF repair is rare and appears to occur only in severely dilated aortas or at areas of previous surgical shunt.[388–390]

In individuals after particular congenital cardiac surgeries, there is a risk of aortic root dilation. These include the Ross operation for aortic valve disease in which the native aortic root is replaced by a pulmonary autograft, the arterial switch operation for D-transposition of the great arteries, and the initial stages of single-ventricle repair with systemic outflow tract reconstruction (eg, Norwood procedure). The aortic root is referred to as a neo-aortic root in these postoperative patients because it consists mainly of pulmonary arterial root tissue. This pulmonary arterial tissue appears to respond to the high-pressure left-sided system with progressive dilation by the time the individual reaches adulthood. A dilated neo-aortic root is seen in half of patients with arterial switch operation[391] and in nearly all patients after hypoplastic left heart syndrome[392] in adulthood. Aortic insufficiency without stenosis, older age at the time of surgical correction, and, for patients with arterial switch operation, presence of a ventricular septal defect, previous pulmonary artery banding, and the association with coexisting CoA are associated with increased neo-aortic dilatation.[393,394]

### *Diagnosis and Management*

The standard for aortic assessment in CHD remains echocardiography before cardiac MR or CT.[395] For each of these ACHD populations at risk for aortic dilation, including the postsurgical populations, active aortic surveillance is recommended at an ACHD center for follow-up. New aortic regurgitation on physical examination may signal aortic root dilation and would warrant echocardiography if recent imaging has not been undertaken. The 2008 American College of Cardiology/AHA guidelines for ACHD recommend aortic imaging every 5 years in patients with CoA. However, other disease states can be imaged at intervals deemed appropriate by the ACHD clinician and team.[2]

## Endothelial Dysfunction and Arterial Stiffness

### *Prevalence and Pathogenesis*

Arterial compliance and endothelial function have increasingly entered the research realm in ACHD. Just as

many diagnoses carry clinical manifestations of arterial vascular disease, the subclinical assessment of the pathophysiology is revealing unique abnormalities in many of the seemingly heterogeneous congenital diagnoses.[396–398] To date, CoA is the best-studied vascular phenotype and presents the panoply of challenges in vascular assessment and management. Individuals with CoA have endothelial dysfunction that persists despite successful repair in many individuals, including those without hypertension. There may be a subset of patients with normal endothelial function,[399] suggesting that a subset of individuals with CoA may have a more concerning vascular risk profile. The contribution of endothelial dysfunction to coronary arterial disease is not yet known, but there are existing markers of subclinical atherosclerosis, including increased carotid and femoral intima-media thickness in the adult CoA population.[400] Central aortic stiffness is also markedly increased and associated with increased left ventricular mass in normotensive young subjects after successful early repair of CoA,[401] and fluid dynamics modeling has revealed that ventricular-vascular coupling hemodynamics determine the effects of intervention on myocardial strain.[402]

Patients after Fontan palliation are another population at risk for endothelial dysfunction.[403,404] The lack of pulsatility in the lung alters the endothelium-dependent vasorelaxation response of the pulmonary arteries, which can have profound effects on vascular recruitment and lung vessel growth.[405,406] The consequences of these changes may adversely influence pulmonary vascular resistance. Furthermore, impaired endothelial function and increased arterial stiffness may also contribute to increased systemic vascular resistance in patients with Fontan physiology.[407]

These data, although not yet clinically applicable en masse, provide valuable new mechanisms to evaluate vascular physiology in ACHD that may influence future clinical practice.

## Hypertension

### *Prevalence and Pathogenesis*

There may be an increased risk of hypertension in the ACHD population compared with the general population,[8] especially among men.[280] Quebec CHD database figures showed a prevalence of 47% in a CHD population comprising people >65 years of age.[4] Adults with CHD and renal abnormalities (cyanotic CHD, heart failure with renal insufficiency) and patients with CoA, who may have systemic hypertension despite abolition of a coarctation gradient, are particularly at-risk populations. Nearly 60% of individuals with CoA develop hypertension.[408] Obesity is associated with the development of hypertension, insulin resistance, dyslipidemia, sleep apnea, autonomic imbalance, and increased inflammatory cytokines.[307]

### *Management*

Management of hypertension in the adult with CHD mirrors the general adult guidelines for blood pressure management.[409] Diagnostic evaluation includes assessment of target organ damage and noncongenital reasons for hypertension. Urinalysis, blood glucose levels, hematocrit, lipid panel, basic metabolic panel, and calcium levels are obtained. Identifiable causes of hypertension such as sleep apnea, nonsteroidal anti-inflammatory drug use, CKD, endocrine causes, renovascular disease, and CoA should be considered. The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among people with CHD remain uncertain. SPRINT (Systolic Blood Pressure Intervention *Trial*) revealed that among adults without CHD (>50 years of age) and at high risk for cardiovascular events but without DM, targeting a systolic blood pressure of <120 compared with <140 mm Hg resulted in lower rates of fatal and nonfatal major cardiovascular events and death resulting from any cause.[410] Current guidelines for blood pressure goals may be extrapolated to adults with CHD, with particular attention to those individuals in whom a lower afterload (eg, systemic right ventricle, single ventricle, aortic dilation) would be beneficial. However, in SPRINT, rates of hypotension, syncope, electrolyte abnormalities, and acute kidney injury were higher with intensive treatment, and attention to the risk of those adverse events in individuals with CHD, especially the moderate to complex diagnoses, is important when blood pressure goals are extrapolated.[410] Lifestyle modifications include a focus on salt intake and attention to obtaining a healthy BMI because obesity increases the risk of premature vascular disease, DM, and hypertension.[307] Physical activity should be encouraged as tolerated, and actual exercise prescriptions should provide clear guidelines for patients. Changes in aortic stiffness, diameter, and wave reflection that can occur with aging may lead to increased ventricular afterload, resulting in potential adverse effects in late systolic ejection and diastolic relaxation. In these individuals, blood pressure management, afterload reduction, and prevention of adverse ventricular remodeling may help clinicians target the correct medical regimen for their individual patient. Management with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in combination with a mineralocorticoid receptor blocker such as spironolactone or eplerenone may have a cardioprotective benefit.[411]

# PSYCHOSOCIAL

## Prevalence

Adults with CHD are at increased risk of psychological distress, neurocognitive deficits, and social challenges.







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Three North American studies published between 2000 and 2009 that incorporated clinical interviews reported that approximately one third of adults with CHD had mood or anxiety disorders.[412–414] Traditionally, depression is the psychiatric disorder that has received the majority of attention within general cardiology and congenital cardiology,[2,415] although anxiety is increasingly recognized. In patients with CHD presenting for psychological services, anxiety concerns were observed to be more prominent than mood disturbance.[416] In another sample, 20% of patients with CHD reported symptoms consistent with posttraumatic stress disorder.[417] Thus, it is important to be mindful of the potential for both mood and anxiety disorders when considering the psychological impact of living with CHD.

Children and adolescents with CHD are at elevated risk of neurodevelopmental deficits, and the frequency and severity increase with greater disease complexity.[418] Young patients with CHD have an increased prevalence of neurodevelopmental disabilities, deficits in behavior, language and speech disorders, and attention-deficit/hyperactivity disorder and increased use of special services.[418,419] Deficits in executive functioning are common[420,421] and present challenges in planning and behavioral regulation. A rich body of research in the pediatric CHD setting exists, although we know far less about neurocognitive outcomes of adults with CHD.[307,422,423] Although intelligence scores for adults with CHD generally fall within the normal range,[424–426] deficits in executive functioning have been observed.[427,428] It has been suggested that the manifestation of pediatric-onset neurocognitive deficits might become more evident in adulthood and that adult-onset factors (eg, heart failure, arrhythmias) might negatively affect cognitive functioning.[423]

Consistent with a psychosocial conceptualization, the social impact of living with a chronic medical condition should not be minimized. It is not uncommon for adults with CHD to report difficulties with social interactions, conflicting social expectations, and "feeling different" from their peers.[429,430] Recalled parental overprotection has been associated with heart-focused anxiety in adulthood.[431] Furthermore, loneliness and social anxiety have been linked to low mood and generalized anxiety among adults with CHD.[414] Higher education, employment, independent living, and being married have been associated with better quality of life among adults with CHD.[432,433] As a group, however, adults with CHD, particularly those with more complex forms, tend to have lower educational attainment and higher rates of unemployment.[434–436]

Furthermore, there may be specific challenges associated with romantic relationships, sexuality, and family planning.[437] Compared with healthy peers, adults with CHD are less likely to be involved in romantic relationships.[438] Many patients are embarrassed by surgical scarring.[439] Among adults with CHD with implantable cardioverter-defibrillators, greater shock anxiety has been associated with poorer sexual functioning.[440] Therefore, CHD has the potential to affect patients' education, employment, relationships, and sexuality and thus overall psychosocial well-being.

## Pathogenesis

The pathogenesis of psychosocial distress in adulthood for individuals with CHD is multifactorial. The time period during which individuals with CHD transition from adolescence to young adulthood is one in which mental health warrants particular attention. In the general population, three quarters of mental health disorders present by the age of 24 years.[441] Young adults with CHD may face a number of unique biopsychosocial challenges.[442] This list includes factors related to medical care (eg, ongoing medical surveillance, transitioning from pediatric to adult care, adjusting to implanted cardiac devices, making treatment decisions, preparing for repeat intervention, declining physical health), cognitive challenges (eg, lower academic abilities and achievement, negative thinking), and social functioning (eg, loneliness, social anxiety, parental overprotection, body image concerns, autonomy).[414,430,431,442–447] No definitive conclusions can be drawn with regard to whether psychosocial distress differs by age, sex, or defect complexity.[430] Perceptions of health might be more germane to emotional well-being than objective health status.[414,448] With regard to neurodevelopmental outcomes, the causes are again multifactorial and include circulatory abnormalities that affect the heart and brain development, medical and surgical intervention, and comorbid syndromes or genetic disorders.[418]

Furthermore, a subgroup of patients have genetic syndromes that place them at greatly elevated risk of mental health disorders. Individuals with conotruncal heart defects have a higher prevalence of 22q11.2 deletion syndrome, and this genetic syndrome in turn is associated with significantly higher rates of mental health disorders, including schizophrenia.[449,450]

## Management

Effective management entails the identification of individuals experiencing clinically significant psychosocial distress and the provision of targeted interventions. Within empirical studies, there is known variability in the surveys that researchers have used to assess psychosocial distress, a situation that has certainly contributed to inconsistent findings.[451] Published guidelines for both coronary artery disease and CHD have recommended screening for depressive symptoms during clinical encounters.[2,452] However, as previously described, an exclusive focus on depression will fail to

identify patients with anxiety problems. Furthermore, there is no clear evidence that routine screening for depression in cardiac patients improves mood or cardiac outcomes.[453] Before the implementation of formal screening programs, it is important to ensure that there are adequate resources to score the chosen measure, discuss results with patients, and provide mental health care to patients with both elevated distress and an interest in treatment.

The "4 As" have been suggested as a strategy for regional ACHD programs to address the psychosocial challenges faced by many of their patients.[442] The 4 components are the following: (1) ask patients about specific challenges, (2) advise about common challenges that are likely to occur and ways they can be managed, (3) assist the patient through education and brief problem solving, and (4) arrange referrals to mental health professionals as appropriate. Within this approach, mental health professionals are 1 part of a comprehensive approach, and all CHD care providers (physicians, advanced care providers, and nurses) have the opportunity to provide proactive care. It is of benefit for all providers in the healthcare team to demonstrate increased psychosocial awareness and to initiate proactive discussions that normalize common concerns.[442]

Quantitative and qualitative research has indicated that, as a group, adults with CHD are interested in mental health treatment and opportunities for peer support.[430,454] We anticipate that adults with CHD will increasingly advocate for attention to their mental healthcare needs in recognition that living with a lifelong cardiac condition affects more than a person's heart.

Many patients would benefit from mental health evaluation and treatment. However, most adults with CHD with mood or anxiety disorders do not receive treatment.[412–414] Regional ACHD centers must determine the most appropriate and feasible approach for the identification and management of psychosocial distress in their patients. Although the optimal approach is the integration of mental health professionals within care teams, this is not always realistic, and other options include collaborating with mental health professionals within a program's hospital or university or identifying providers in the local community.[443]

Specific approaches to psychotherapy (talk therapy) include cognitive behavioral therapy, interpersonal therapy, acceptance and commitment therapy, and mindfulness-based interventions. A study to determine the feasibility of conducting a randomized controlled trial of a group coping skills intervention has been introduced.[455] Among children with CHD, there are no clear relationships between physical activity and the psychosocial domain of quality of life.[456] However, because physical activity has proven benefits for adults identified as being depressed or anxious,[457] the encouragement of medically appropriate physical activity, with potential for both physical and psychosocial benefits, appears appropriate.

In a sample of 134 respondents who were asked about preferences for future mental health treatment, 41% preferred psychotherapy, 9% preferred pharmacotherapy, and 34% found either approach acceptable.[454] Thus, although psychotherapy may be generally preferred, pharmacotherapy represents another approach to be considered for adults with CHD, particularly for those who prefer this modality or for whom access to psychotherapy is limited. Compared with other types of antidepressants, selective serotonin reuptake inhibitors have been shown to be safest in treating depression in adults with cardiovascular disease.[458–460]

Within the pediatric CHD setting, algorithms for the screening, surveillance, and management of neurodevelopmental deficits and disorders have been proposed, and many pediatric cardiology centers have established neurodevelopmental follow-up clinics.[418] Opportunities for comprehensive neurocognitive assessment are currently much rarer in the adult care environment. What is likely more feasible, but admittedly requires additional time in already busy clinic visits, is inquiry about the patient's academic history (eg, previous diagnosis with a learning disorder or attention-deficit/hyperactivity disorder, history of special education classes) and employment history (eg, difficulty obtaining or maintaining employment).[423] A thoughtful consideration of the use of medications for attention-deficit/hyperactivity disorder is required on an individual patient basis.[461] Education and vocational education, in adolescence and young adulthood, are warranted.

## NONCARDIAC SURGERY

CHD is a heterogeneous group of defects leading to unique risk factors for surgery among the different cardiac lesions. The combination of complex heart disease and associated noncardiac conditions places adults with CHD at greater risk than the general population for noncardiac surgery.[22,462–464] Guidelines for perioperative cardiovascular risk assessment in the general population focus primarily on the risks posed by ischemic heart disease, which is relatively uncommon in adults with CHD.[465] As discussed throughout this document, adults with CHD have multiorgan involvement, which places them at risk for perioperative complications. Although patients with CHD are at increased risk when undergoing noncardiac surgery, up to 74% of noncardiac surgeries in ACHD patients occur at non-ACHD centers.[466] Ideally, elective noncardiac surgery would take place in a regional ACHD center with specialists familiar with and experienced in the management of those with CHD (Figure 2).[2]







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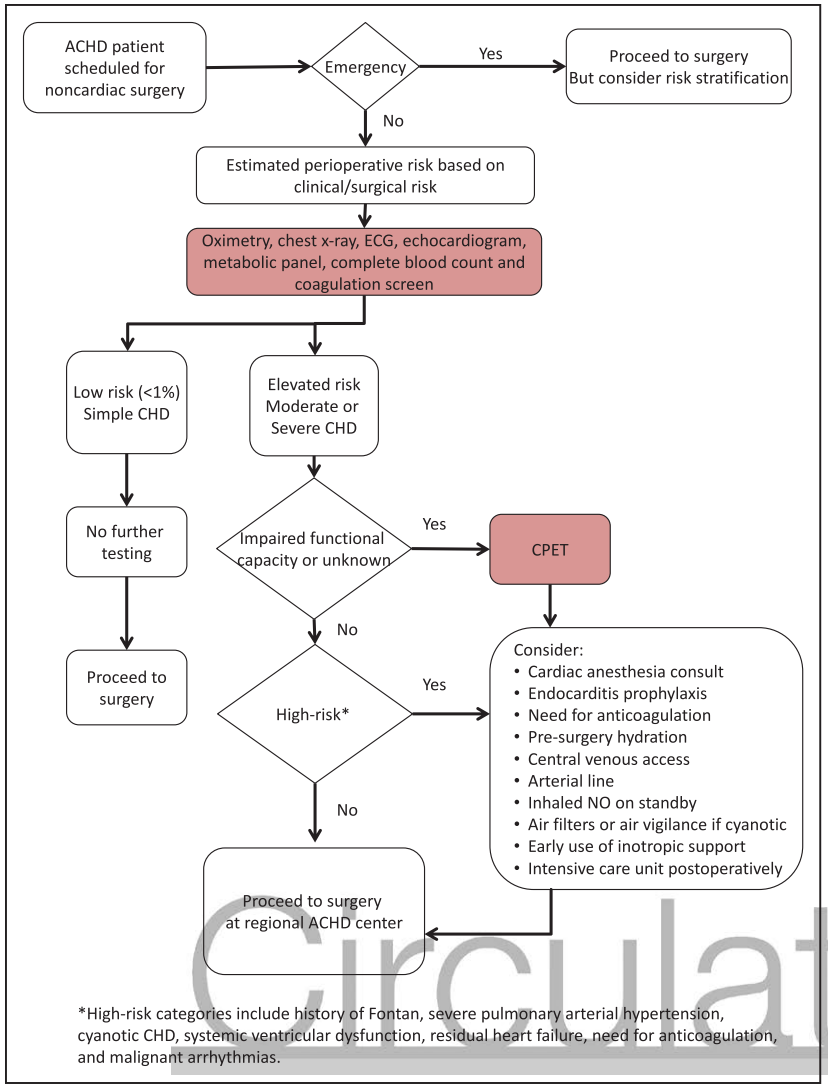


**Figure 2. Stepwise approach to perioperative cardiac assessment in adults with congenital heart disease (CHD).**
ACHD indicates adult congenital heart disease; CPET, cardiopulmonary exercise test; and NO, nitric oxide. Adapted from Warnes et al.[2] Copyright © 2008, American Heart Association, Inc.





## Preoperative Evaluation

A comprehensive preoperative assessment is essential in the care of adults with CHD undergoing noncardiac surgery. Residual cardiac abnormalities such as ventricular dysfunction, valvular dysfunction, pulmonary hypertension, arrhythmia, or shunts place patients with CHD at high risk for intraoperative and postoperative complications.[467–469] Before any elective surgery, a complete understanding of the patient's previous cardiac surgeries and current cardiac physiology is required to better perform adequate risk assessment for the upcoming surgery. Inadequate preoperative assessment and optimization accounts for up to 40% of the adverse events in adults with CHD who undergo noncardiac surgery.[470] Patients with certain complex cardiac lesions such as severe pulmonary hypertension or Eisenmenger syndrome have a very high risk for adverse outcomes during noncardiac surgery, with mortality ranging from 4% to 10% in the modern era.[462,471,472] Those with Fontan palliation for single-ventricle anatomy have also been shown to have a much higher than normal complication rate, with some series having complication rates as high as 31%.[463]

Preoperative risk assessment before noncardiac surgery in the patient without CHD emphasizes the use of functional capacity to determine the patient's risk for perioperative complications.[465,473] However, many adults with CHD have adapted to lifelong decreased functional capacity by self-restricting activity and report that their functional status is unchanged or fine when questioned. Exercise testing can objectively measure functional capacity and cardiac reserve and has an increased role in preoperative evaluation of patients with CHD compared with in the general population.

Arrhythmias are common in the perioperative setting, with ≈50% of adults with CHD having some rhythm disturbance.[474] Antiplatelet or therapeutic anticoagulants are often used for stroke prevention in patients with CHD with arrhythmias, residual shunts, prosthetic

valves, or previous thromboembolism. The risks of withholding these agents and subsequent thromboembolic events must be considered for each noncardiac surgery. The 2014 American College of Cardiology/AHA guidelines on perioperative cardiovascular evaluation provide an algorithm for antiplatelet management in patients with previous coronary intervention who are undergoing noncardiac surgery.[465] For patients with mechanical heart valves, bridging anticoagulation may be appropriate in the setting of mechanical atrioventricular valve or mechanical aortic valve with ≥1 additional risk factors (eg, atrial fibrillation, previous thromboembolism, systemic ventricular dysfunction, hypercoagulable condition, or an older-generation prosthetic aortic valve).[465] Vitamin K and fresh-frozen plasma can reverse warfarin for urgent or emergent noncardiac surgery. In patients with CHD with arrhythmias, residual shunts, or aortic prosthetic valves without risk factors, antiplatelet or vitamin K antagonists may be discontinued 2 to 3 days before surgery. Factor Xa inhibitors should be discontinued at least 48 hours before major surgery.[465] The 2014 American College of Cardiology/AHA guidelines suggest monitoring activated partial thromboplastin time for dabigatran and prothrombin time for apixaban and rivaroxaban.[465]

The pulmonary sequelae of CHD can complicate the perioperative management and increase surgical risk. In 1 study, 56% of adults who underwent heart surgery in childhood had restrictive lung disease, which affects ventilator management and extubation.[59] Certain complex lesions such as heterotaxy syndrome have cilia dysmotility, increasing the risk of postoperative pneumonia and prolonged ventilation.[475–477]

Many patients have had surgeries that intentionally sacrificed a subclavian artery (classic Blalock-Thomas-Taussig shunt, subclavian flap repair of CoA). These patients often have spuriously low blood pressure in the affected arm. Hence, intraoperative and postoperative blood pressure monitoring must use an appropriate extremity to accurately reflect central aortic pressure. Communication with the anesthesiology, surgical, and nursing teams is critical to ensure that blood pressures accurately reflect central pressures and that patients are not inadvertently administrated vasoactive agents as a result of misleading vital signs.

Many adults with complex CHD have occluded femoral veins or arteries resulting from catheterizations performed in childhood. In addition, systemic venous anatomy may be unusual in the setting of heterotaxy syndrome, a Mustard baffle, or a Glenn shunt. If venous or arterial access is needed for intraoperative monitoring, such anatomy should be documented before surgery. If unknown, preoperative noninvasive imaging is appropriate.

Many patients with CHD have a pacemaker. Epicardial pacing systems are common, and these devices may be located below the diaphragm, requiring accurate knowledge of the device position before abdominal surgery to avoid damage to or infection in the pacing system. For patients who are pacemaker dependent, reprogramming of the device to potentially slightly higher heart rates can be desirable. Pacemakers should be programmed to safe surgical modes to avoid inhibition of the device from electric impulses such as from the electric cautery system.

Patients with CHD are at higher risk for perioperative infections and may require antibiotic prophylaxis for endocarditis as outlined by the AHA guidelines.[463] Most gastrointestinal or genitourinary tract procedures no longer require antibiotic prophylaxis.[177]

## Perioperative Management

Patients with cyanotic heart disease or pulmonary arterial hypertension have extremely high risk, and if surgery is truly elective, it is usually best avoided. Mortality for these patients after noncardiac surgery remains as high as 7% to 10%.[462,471] Those with CHD of moderate complexity but excellent preoperative functional capacity and no more than mild systemic ventricular dysfunction are at lower risk.

For patients with Eisenmenger syndrome, providers must consider the multiple organ systems affected by chronic cyanosis, expected fluid shifts, and bleeding risks. Because of multiple collaterals that develop within tissues, platelet dysfunction, and alterations in the coagulation cascade, cyanotic patients have increased surgical bleeding.[212] Although routine phlebotomy has been mostly abandoned in Eisenmenger syndrome, a role remains for preoperative phlebotomy to decrease surgical risk. Those with a hematocrit above ≈65% should have preoperative isovolumic phlebotomy to reduce intraoperative bleeding and to decrease viscosity, with the removed blood stored for autotransfusion if needed during surgery.[478] Because patients with Eisenmenger syndrome have relatively fixed pulmonary vascular resistance, vigilance and avoidance of conditions that worsen pulmonary vascular resistance are paramount, including the avoidance of hypothermia, metabolic acidosis, hypercarbia, and hypovolemia. Placement of an arterial line to identify such changes early should be considered. Pulmonary arterial catheters may trigger an arrhythmia and cause paradoxical embolism from microthrombi or in situ pulmonary thrombi. Because patients with Eisenmenger syndrome have relatively fixed pulmonary resistance and pulmonary pressure is equal to a noninvasively measure blood pressure, risks often outweigh benefit.[238,479] Central venous catheters also pose risk because these patients are prothrombotic, leading to potential catastrophe if venous thromboembolism occurs in the pulmonary circulation or in the systemic circulation via a residual intracardiac shunt. These risks and benefits of central venous pressure monitoring and ease of intravenous fluid and medication infusion by central line are assessed and







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considered. To avoid air emboli in all venous access, meticulous care with air filters and air vigilance protocols is required. With any hypotension, increased cyanosis will be seen with increased right-to-left shunting; therefore, a thoughtful plan is needed for which agents to use for the induction and maintenance of anesthesia. Some centers will elect to admit these patients the evening before surgery to allow continuous maintenance fluid in the setting of restricted oral intake before surgery.

Patients with Fontan palliation pose unique challenges. The anesthesia team must avoid hypercarbia and acidosis because they increase pulmonary vascular resistance or pulmonary pressures, maintain adequate inferior vena cava pressure, and avoid hypovolemia. Oxygen can still be a potent vasodilator in many of these patients, so higher supplemental oxygen levels are recommended, with the ready availability of inhaled nitric oxide to treat low cardiac output.

Low airway pressure is desirable because higher intrathoracic pressures for prolonged periods will decrease cardiac output in Fontan circulation. Anesthesiologists and respiratory therapists are encouraged to minimize positive end-expiratory pressure to the lowest level required to avoid atelectasis, hypercarbia, and hypoxia. Laparoscopic surgery can be dangerous in patients with Fontan physiology if intra-abdominal pressure rises too high. Whereas intra-abdominal pressures of <15 mm Hg do not appear to adversely affect cardiac performance in patients with 2-ventricle circulation,[480–482] a similar threshold for those with Fontan physiology is not known. Case reports have shown that laparoscopic surgery can be performed with acceptable risk if intra-abdominal pressures are <10 mm Hg in patients with Fontan physiology.[483] Additional care is needed to prevent carbon dioxide embolization to the lungs, which is not tolerated well in these patients, and to avoid paradoxical embolization, which can occur through a persistent Fontan fenestration or right-to-left shunting from venous collaterals.[484–486] Because abdominal insufflation can lead to hypercarbia or increased intrathoracic pressures, either of which may lead to a drop in cardiac output, intra-arterial lines are frequently placed. Central venous access is used for longer procedures with larger volume shifts to allow rapid fluid resuscitation and central venous pressure measurements. Such patients usually also receive preoperative intravenous hydration secondary to their relative volume depletion in the fasting state. Neuraxial anesthetic techniques can be safe in patients with Fontan physiology, which may be particularly useful for obstetric and gynecologic surgery, although careful titration of these agents is needed.[487]

## Postoperative Management

Postoperative monitoring and care are as important as the preoperative assessment and intraoperative management because 50% of adverse events after noncardiac surgery are related to postoperative issues.[470] Common postoperative complications such as bleeding, fever, thromboembolism, infection, or pulmonary edema may affect the patient with CHD with cardiac and noncardiac comorbidities with greater impact than in the average patient. Many patients require either postoperative diuresis or volume resuscitation, depending on the underlying cardiac physiology and the perioperative blood loss. Adults with CHD require close surveillance focused on monitoring for postoperative arrhythmias; postural hypotension, which may exacerbate a right-to-left shunt; pain management; and fluid shifts.[2,462] Patients with Eisenmenger syndrome require observation in the intensive care unit for 12 to 24 hours after noncardiac surgery to address acute changes in pulmonary and systemic resistance.

The reinitiation of anticoagulation and antiplatelets after noncardiac surgery depends on the relative risk of bleeding versus thrombosis. For patients at high risk of thromboembolism, early ambulation and pneumatic compression may prevent DVT. Intravenous heparin and oral anticoagulants can be resumed as soon as determined safe by the surgical team. In patients with a lower risk of thrombotic complications, these agents may be resumed safely several days after the procedure.

## SUMMARY

Noncardiac complications contribute significantly to the morbidity and mortality of adults with CHD. As these individuals grow in number and age, we need to identify preventive strategies with intervention at an earlier age to mitigate the development of later noncardiac complications. Many patients with repaired simple CHD are now in their six or seventh decade of life or later, whereas most patients with complex CHD such as the Fontan circulation are relatively younger. Single-ventricle programs provide an opportunity to care for these individuals with a multidisciplinary team that includes clinicians with expertise in neurodevelopment, hepatology, and nephrology. Although we have made progress, many research questions remain, and considerable work still needs to be done. For example, the role of biomarkers in CHD and their relationships with noncardiac conditions are not well known. Whereas animal models demonstrate that angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists have important antifibrotic effects in end organs (including kidneys, heart, and liver), it is unknown whether these medications confer a protective effect when introduced early. Other questions include the incidence of IE in transcatheter valves, the effectiveness of non–vitamin K antagonist oral anticoagulants in ACHD, risk stratification of patients for pulmonary function tests and noncardiac surgery, and

cancer screening for complex CHD. The effect of chemotherapy on the congenitally abnormal heart is not known. Do patients with right ventricular dysfunction warrant closer monitoring in the setting of chemotherapy? Furthermore, the impact of psychosocial factors on quality of life, mortality, and morbidity warrants investigation. In summary, adults with CHD often have complex multisystemic disease for which both cardiac outcomes and noncardiac complications warrant clinical attention and empirical investigation; an interdisciplinary approach is required across the life span of these patients.

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# Diagnosis and Management of Noncardiac Complications in Adults With Congenital Heart Disease: A Scientific Statement From the American Heart Association

George K. Lui, Arwa Saidi, Ami B. Bhatt, Luke J. Burchill, Jason F. Deen, Michael G. Earing, Michael Gewitz, Jonathan Ginns, Joseph D. Kay, Yuli Y. Kim, Adrienne H. Kovacs, Eric V. Krieger, Fred M. Wu, Shi-Joon Yoo and On behalf of the American Heart Association Adult Congenital Heart Disease Committee of the Council on Clinical Cardiology and Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; and Council on Quality of Care and Outcomes Research

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