



# Impact of Non-cardiac Comorbidities in Adults with Congenital Heart Disease: Management of Multisystem Complications

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## 22.1 Introduction

The prevalence and impact of non-cardiac comorbidities in adult patients with congenital heart disease increase over time, and these complications are often specifically a consequence of the long-term altered cardiovascular physiology or sequelae of previous therapies. For the ACHD patient admitted to the intensive care unit (ICU) for either surgical or medical treatment, an assessment of the burden of multisystem disease, as well as an understanding of the underlying cardiovascular pathophysiology, is essential for optimal management of these complex patients. This chapter takes an organ-system-based approach to reviewing common comorbidities in the ACHD patient, focusing on conditions that are directly related to ACHD status and may significantly impact ICU care.

## 22.2 Pulmonary Disease

Pulmonary disease is a common comorbidity in adult congenital heart disease (ACHD) patients. Among 1200 ACHD patients followed over 7 years, 47% had abnormal lung function, including nearly 30% with moderately to severely reduced forced vital capacity (FVC) associated with a 1.6-fold increased mortality [1]. Similarly, among 2600 ACHD patients followed over 4 years, 18.4% of those that

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died had lung disease versus 5% of those still living [2]. Patients with unrepaired lesions, cyanotic heart disease, single-ventricle palliation, and CHD repaired at an older age have a more significant burden of lung disease [1, 3]. Lung disease is an indication for hospital admission in 5–12% of ACHD patients and accounts for 12–14% of all postoperative readmissions [4, 5]. Furthermore, preoperative lung disease has been found to be a risk factor for longer ICU length of stay, adverse cardiovascular events, and in-hospital mortality [6–11].

### 22.2.1 Airway Abnormalities

Large airway abnormalities such as tracheobronchomalacia, subglottic stenosis, and airway compression, which may be congenital or acquired, can be seen in ACHD patients and may impact risk in the perioperative period or respiratory support requirements in the ICU. Tracheobronchomalacia may be associated with a syndrome such as trisomy 21 or related to chronic lung disease or prolonged mechanical ventilation requiring tracheostomy [12–14].

Tracheal or bronchus compression caused by surrounding cardiac or vascular structures can be seen in ACHD patients. For example, ventricular dilation may result in compression of the left main stem bronchus and surrounding lung tissue [13], and left atrial dilation may cause compression of the main stem bronchi [15]. Distal tracheal and right main stem compressions are frequently seen in the context of left pulmonary artery slings. Vascular rings are associated with tracheomalacia and tracheal compression [16]. Dilated vascular structures, such as pulmonary arteries in the context of severe pulmonary regurgitation or absent pulmonary valve syndrome, can cause compression of the trachea, main stem bronchi, and lung parenchyma and may be accompanied by emphysematous changes [13].

Knowledge of a patient's airway and mechanical ventilation history may suggest underlying structural airway defects and inform decisions on ventilation strategy and postoperative lung recruitment. Preoperative airway assessment by noninvasive imaging or direct laryngobronchoscopy may guide a patient's management around intubation, including choice of sedative/induction agents and available equipment and personnel resources. Additionally, structural airway abnormalities may warrant higher positive-pressure ventilation, positive end-expiratory pressure (PEEP) in particular, to maintain ventilation around functional residual capacity. Noninvasive positive-pressure ventilation and aggressive pulmonary toilet may be required after extubation. Lastly, providers should be aware of the risk of post-obstructive pneumonia.

### 22.2.2 Respiratory Infections

Pneumonia affects 10–20% of patients in the cardiac ICU after cardiac surgery [17, 18]. The CONCOR study, which examined 6900 ACHD patients in a Dutch national registry, revealed that 4% of deaths in ACHD patients were secondary to pneumonia,

although the overall mortality rate of the population was low [19]. Risk factors for respiratory tract infections particularly relevant to ACHD patients include underlying immunodeficiency or leukocyte wasting (see section on infectious diseases), chronic malnutrition, airway abnormalities, and history of vocal cord paresis increasing aspiration risk. Malnutrition in particular results in depressed immune function and muscle wasting with consequent poor respiratory effort and atelectasis, also increasing the risk of prolonged mechanical ventilation and impaired airway clearance.

A high suspicion for respiratory infections should be maintained for ACHD patients in the ICU, and infections should be treated aggressively. In addition, preventative efforts such as optimization of nutrition, use of aspiration precautions (elevation of head of bed), and attention to oral hygiene in intubated patients should be maintained. Judicious use of gastric acid-suppression medications should be employed, as these may increase a patient's risk of airway colonization with reflux and aspiration [13, 20].

### 22.2.3 Restrictive Lung Disease

Sequelae of prior cardiac surgeries, including diaphragmatic paralysis, seen in up to 10% of patients with CHD after surgery [21, 22], and chest wall abnormalities, may result in restrictive lung disease. Diaphragm paralysis results in elevation of the hemidiaphragm, decreased lung excursion, and atelectasis and is an independent predictor of moderately to severely depressed FVC (odds ratio 4.64) [1]. Chest wall abnormalities due to scoliosis and prior thoracotomies also independently predict moderately to severely impaired lung function (odds ratio 3.2 and 1.9, respectively) [1]. The presence of scoliosis may result in reduced lung volumes on the side of the greater curvature, reduced number of alveoli and a proportional increase in “remnant alveolar” space closer to the spinal curvature, and abnormal development of the muscles of respiration [23, 24]. Therefore, the presence of scoliosis should factor into decisions regarding ventilation expectations and strategies to maintain adequate lung expansion. Scoliosis may complicate neck mobilization and airway visualization, possibly requiring specialized personnel and equipment for successful laryngoscopy and intubation [25–27].

### 22.2.4 Pulmonary Edema

Interstitial edema, a nearly ubiquitous concern with ACHD patients at some point in their clinical course, decreases lung compliance, requiring the patient to increase their work of breathing to maintain adequate minute ventilation. Pulmonary edema also disrupts the alveolar-capillary interface and impairs gas exchange, decreasing total lung capacity, impairing diffusion, and resulting in hypoxemia. The intraparenchymal airways may be compressed by edema of the peribronchial wall or vessels (“peribronchial cuffing”), leading to an obstructive pattern of lung disease [13, 28, 29].

Furthermore, chronic interstitial edema may cause fibrosis and hypertrophy of lung tissue, resulting in a restrictive lung disease pattern [1].

Pulmonary edema may result from an excess of pulmonary blood flow, as seen in intracardiac (ASD, VSD, PDA, partial anomalous pulmonary venous return) or extracardiac left-to-right shunt lesions (PDA, systemic arteriovenous malformations, aortopulmonary collateral vessels, and surgical aortopulmonary shunts). Pulmonary edema is also seen in lesions associated with high pulmonary venous pressures, including obstruction to left heart inflow (pulmonary vein stenosis or occlusive disease, cor triatriatum), obstruction to left heart outflow (mitral or aortic stenosis), and left atrial volume overload (mitral regurgitation or left ventricular systolic and diastolic dysfunction) [1, 13] requiring careful attention to diuresis and volume management in the cardiac ICU [13]. Interventions that result in pulmonary vasodilation, such as treatment with nitric oxide, sildenafil, or other vasodilators, can worsen pulmonary edema, particularly in the presence of a left-to-right shunt lesion.

Patients with elevated central venous pressures or obstruction to systemic venous drainage may also develop pulmonary edema and pleural effusions. Similarly, extracardiac abnormalities such as superior vena cava syndrome, innominate vein thrombosis, and primary lymphangiectasia may contribute to pulmonary edema and chylothoraces [13]. In addition to volume management and diuresis, these patients may require procedural interventions to alleviate their right heart or central venous obstruction or right ventricular afterload reduction strategies, including reduction of mean airway pressure during ventilation and pulmonary vasodilators, to lower central venous pressures.

Cardiopulmonary bypass also contributes to pulmonary edema in the postoperative ACHD population. The reduction in pulmonary blood flow during cardiopulmonary bypass and exposure to the artificial surfaces of the bypass circuit triggers a diffuse inflammatory response, characterized by cytokine release and pulmonary interstitial leukocyte infiltration, that results in pulmonary capillary leak and transudative edema [1, 30–34]. Attention to diuresis and ventilation strategies to minimize V/Q mismatch are therefore important in the postoperative period.

### 22.2.5 Other Lung Diseases

Acute respiratory distress syndrome (ARDS) is associated with significant early postoperative mortality in adults with ACHD [11]. The typical management strategies used in non-CHD patients, such as high-frequency oscillatory ventilation and high levels of PEEP, may be poorly tolerated in ACHD patients with single-ventricle physiology with passive pulmonary blood flow (Fontan circulation) or with predominantly right-sided heart disease. Strategies to minimize mean airway pressure should be employed where possible. Extracorporeal membrane oxygenation (ECMO) support may be an alternative therapy for this group of patients, although limited data are available on the outcomes of ECMO support for adult Fontan patients.

Adults with CHD may present with typical comorbid pulmonary conditions, including asthma, chronic obstructive lung disease, or emphysema, and these patients may benefit from usual treatments such as bronchodilator therapy, as well as aggressive pulmonary toilet and incentive spirometry to avoid further exacerbation of the lung disease. Other considerations for ACHD patients include pulmonary hypoplasia, a history of tobacco use, and recurrent chest infections, which may result in some degree of parenchymal lung disease.

Lastly, sleep-disordered breathing may be more prevalent in the ACHD population [35–37], related to airway abnormalities or craniofacial abnormalities, such as micrognathia, seen in genetic conditions such as 22q11.2 or Noonan syndromes. Patients with trisomy 21 may also be at increased risk of central sleep apnea [38]. Given that sleep-disordered breathing has been associated with pulmonary hypertension, ventricular dysfunction, and increased morbidity and mortality in patients with heart failure [39–41], noninvasive positive-pressure ventilation should be used in ACHD patients with known sleep-disordered breathing. Preoperative polysomnography should be considered in patients with a history suggestive of sleep-disordered breathing.

### **22.2.6 Pulmonary Considerations in Patients with Single-Ventricle Physiology**

Notable pulmonary considerations exist for ACHD patients with single-ventricle heart disease. In a study of 52 patients with Fontan palliation over 10 years, 58% of patients demonstrated some degree of restrictive lung disease on pulmonary function testing [42]. This may be due to chest wall abnormalities due to multiple thoracotomies and scoliosis, a history of chronic pulmonary edema, recurrent infections and effusions resulting in fibrosis, and some degree of pulmonary hypoplasia due to the lack of pulsatile flow in the Fontan circulation [43].

Patients with Fontan circulation may develop progressive hypoxemia due to development of systemic to pulmonary venous collaterals related to elevated central venous pressures and venous stasis [13] and to arteriovenous malformations due to exclusion of putative hepatic factor. Chronic hypoxemia or structural pulmonary arterial disease in turn may promote development of aortopulmonary collateral vessels which may contribute to chronic pulmonary edema. Pulmonary edema is also exacerbated by activation of the renin-angiotensin-aldosterone axis in low cardiac output states as well as low oncotic pressures in those patients with protein-losing enteropathy (PLE) or malnutrition [13].

Aortopulmonary collateral vessels and arteriovenous malformations also predispose to pulmonary hemorrhage and hemoptysis. Similarly, Eisenmenger syndrome can be complicated by hemoptysis, found to be the cause of death in 11–30% of patients [44, 45]. Pulmonary embolism, due to low-flow state, venous stasis in the Fontan baffle, and baseline prothrombotic state, is also common in the single-ventricle patient population, with pulmonary embolism and chronic pulmonary embolic disease affecting 5–16% of patients [46].

Plastic bronchitis is a rare complication in the Fontan population characterized by acellular, noninflammatory casts that can result in obstructive pulmonary disease and worsening of baseline hypoxemia. It is at least in part due to elevated central venous pressures resulting in impaired lymphatic drainage and decompression into the pulmonary bed. In a study of nearly 1100 ACHD patients, 1.5% of patients were diagnosed with protein-losing enteropathy or plastic bronchitis [47]. Consultation with a pulmonologist should be considered to assist in management of casts, including aggressive pulmonary toilet in those patients who are breathing spontaneously. Treatment options in the cardiac ICU include aerosolized hypertonic saline or heparin or r-TPA nebulizer treatments to disrupt the casts and allow patients to more easily mobilize their secretions. Direct cast removal by bronchoscopy may be required in intubated patients. Beta agonists, mucolytics, expectorants, and dornase alfa administration have not shown efficacy in treating plastic bronchitis [48].

Lastly, ventilation of Fontan patients can be complicated due to competing needs of higher positive end-expiratory pressure to overcome obstructive pulmonary physiology and lower mean airway pressure to promote flow through the Fontan pathway. In the presence of a Fontan fenestration or baffle leaks, higher mean airway pressure may result in worsening of baseline hypoxia due to right-to-left shunt. Without a fenestration or baffle leak, cardiac output may be impaired due to reduced preload to the systemic ventricle. The increase in Fontan pressures due to higher positive airway pressures can lead to ascites and pleural effusions, further impairing ventilation thus requiring even higher positive airway pressures. The effects are amplified when respiratory acidosis leads to increased pulmonary vascular resistance, thereby causing further increase in Fontan pressures. Cautious drainage of ascites and pleural effusions may be beneficial in this situation.

### **22.2.7 Pulmonary Management Strategies**

Cardiopulmonary interactions based on the underlying cardiac lesion must be considered when choosing a ventilation strategy for any ACHD patient admitted to the ICU. Patients with chronic left atrial hypertension, parenchymal lung disease, a history of smoking, frequent chest infections, chest wall deformities, or airway abnormalities may require higher positive-pressure ventilation [49]. Challenges to ventilation of single-ventricle patients, in particular those with Fontan circulation, have been covered in previous sections. Preoperative or routine outpatient pulmonary function testing and early consultation with a pulmonologist should be entertained in at-risk patients, particularly those with right ventricular disease, single-ventricle physiology, or cyanotic heart disease. Due to the myriad of possible pulmonary abnormalities in the ACHD population, all adult patients in the CICU should receive aggressive pulmonary toilet, ambulate early, and use incentive spirometry frequently.

### 22.3 Renal Disease

Renal dysfunction is highly prevalent in the ACHD population and can significantly impact care in the ICU. Among 1100 ACHD patients, 50% had an abnormal glomerular filtration rate (GFR) at baseline, with 9% having moderately to severely impaired GFR. For ICU patients, the presence of renal dysfunction is associated with a threefold increased risk of overall mortality and is predictive of poor postoperative outcomes [11, 50–52]. In a cohort of nearly 2600 ACHD patients over 4 years, approximately 21% of deceased patients had some degree of renal disease compared to only 3% of survivors [2]. Risk factors for renal disease include more complex congenital heart lesions, history of multiple surgical interventions, and persistent cyanosis [53]. Patients with univentricular and right ventricular disease, as well as Eisenmenger syndrome, are at a heightened risk of having moderately to severely depressed renal function, at least in part related to chronic elevation of central venous pressures [50, 51, 54].

In addition to the risk of baseline chronic renal insufficiency, ACHD patients are at increased risk of developing acute kidney injury (AKI) during hospitalizations. Estimates of any AKI in the postoperative period range from 36 to 59% [55] and of renal failure or moderate to severe AKI from 5 to 20% [55, 56]. Pre-existing renal dysfunction is a risk factor for longer length of hospitalization and postoperative readmission in ACHD patients [4, 57], though renal failure requiring renal replacement therapy is uncommon [10].

Renal dysfunction may be caused or exacerbated by several factors in the ICU. Hypothermia, hypotension, and bleeding during cardiopulmonary bypass (CPB) may all impair renal perfusion, with longer duration of CPB associated with higher risk of renal dysfunction [58]. Fluid overload may contribute to increased central venous pressure (CVP) and, therefore, decreased renal perfusion pressure. Renal dysfunction may be potentiated by factors that decrease cardiac output, including ventricular dysfunction and arrhythmias [53].

A decrease in renal perfusion pressure, the difference between the mean arterial pressure and central venous pressure, can lead to deterioration of renal function. Thus, congenital lesions with high central venous pressure, such as right ventricular lesions (e.g., tetralogy of Fallot) and single-ventricle circulation, are more commonly associated with renal dysfunction [53]. High central venous pressures may also contribute to development of ascites, causing abdominal compartment syndrome; high intra-abdominal pressures further increase CVP and therefore further reduce renal perfusion pressure. Ascites also limits downward movement of the diaphragm, necessitating higher-pressure ventilation, which further elevates right heart pressures and CVP. This increase in CVP leads to further reduction in renal perfusion pressure as well as decreased systemic venous return, potentially resulting in a low cardiac output state and further reduction in renal perfusion [59–61].

### 22.3.1 Renal Management Strategies

Given the morbidity and mortality associated with renal dysfunction in this patient population, preservation of renal function must be a priority. Preoperative assessment of renal function in high-risk patients by creatinine clearance calculation or renal scintigraphy allows risk stratification, anticipation of potentially nephrotoxic exposures, and employment of protective strategies when possible [53]. These strategies should include careful monitoring of a patient's hemodynamics with avoidance of hypotension and maintenance of renal perfusion pressure. Monitoring of bladder pressure has resulted in reduced incidence of abdominal compartment syndrome in non-ACHD patients and may be appropriate in those patients at highest risk for intra-abdominal hypertension [62]. Additionally, careful drainage of ascites may be appropriate in certain patients to relieve intra-abdominal hypertension, improve renal perfusion pressure, improve systemic venous return, facilitate effective positive-pressure ventilation, and maintain cardiac output [53].

Nephrotoxic agents, including iodine-based contrast, should be avoided when possible, and medications should be appropriately dose-adjusted based on either measured or estimated GFR when required. Specific considerations include dose adjustment of milrinone in patients with reduced GFR as well as avoidance of angiotensin-converting enzyme inhibitors in patients with risk of impaired renal perfusion or acute kidney injury. Medications that cause peripheral vasoconstriction and could potentially diminish renal perfusion, such as norepinephrine and vasopressin, should be avoided when possible [53]. A meta-analysis of fenoldopam administration during cardiopulmonary bypass in non-ACHD patients revealed reduced utilization of renal replacement therapy, shorter duration of stay in the intensive care unit, and decreased overall in-hospital mortality. Although there are no data on the use of fenoldopam in adults with CHD, it may be an appropriate drug to consider in those patients with baseline renal dysfunction or those at high risk of developing acute renal impairment in the cardiac ICU [63].

Contrast nephropathy prevention strategies, including the use of fenoldopam, N-acetylcysteine, and sodium bicarbonate, are controversial and insufficiently examined in the ACHD population. Studies have not demonstrated a decrease in contrast-induced nephropathy in non-ACHD patients with baseline renal dysfunction treated with fenoldopam [64]. Several studies have demonstrated reduction in contrast-induced nephropathy rates in patients treated with sodium bicarbonate and N-acetylcysteine but have failed to demonstrate a statistically significant decline in renal failure requiring renal replacement therapy [65, 66]. Despite their controversial nature, it may be reasonable to consider the use of contrast nephropathy prevention in those patients with significant baseline renal disease and those at highest risk for development of renal dysfunction in the ICU.

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### 22.4 Infectious Disease

Infection accounts for significant morbidity and mortality in the ACHD population, with postoperative infection occurring in approximately 15% and septicemia in 7% of patients [4, 56]. Deaths of ACHD patients in the perioperative period were



attributed to sepsis in 4% of cases [2]. In a study of nearly 100,000 hospitalized ACHD patients, septicemia was associated with the longest length of stay [57]. The risk of CLABSI in ACHD patients may be increased by a patient's limited venous access due to prior procedures, necessitating longer central venous catheter placement.

General infection risk may be increased by multifactorial immunodeficiency as well as prior colonization by hospital-acquired organisms, leading to nosocomial infections. First, several syndromes commonly associated with CHD, such as heterotaxy with asplenia, 22q11.2 deletion syndrome, and trisomy 21, are associated with varying degrees of immune dysfunction. Second, many adults who have undergone cardiac surgery in childhood may have undergone a complete or partial thymectomy [67], which, although associated with lower absolute T-cell numbers and T-cell subsets, is not associated with overt immunodeficiency [68]. Lastly, ACHD patients may have chronic wasting of immunoglobulins and lymphocytes due to thoracic duct injury or inadequate lymphatic drainage with resultant chylous effusions [69].

### 22.4.1 Immune Abnormalities in Single-Ventricle Palliations

T-cell lymphopenia and hypogammaglobulinemia may be seen in single-ventricle patients with protein-losing enteropathy (PLE). Chronic systemic venous hypertension impairs lymphatic drainage into the venous circulation, resulting in dilatation of the lymphatic channels and collateral formation to allow drainage into lower resistance reservoirs, such as the intestine [67, 70, 71]. Although patients with PLE have the most profound abnormalities, patients without overt PLE may also have some degree of lymphopenia, presumably due to a chronic low level of protein wasting [67, 72]. These abnormalities are more pronounced later after Fontan operation, with a fourfold increase in the odds of significant lymphopenia in the second decade after Fontan [67]. Depressed immunoglobulin G levels are also found in patients with PLE with an associated impaired response to the pneumococcal, diphtheria, and tetanus vaccines. Despite this, PLE is not associated with an increased risk of opportunistic infections, nor is it a risk factor for hospitalization for infection [67, 72]. Although not a risk factor in isolation, in the ICU setting, it is important to recognize the potential for baseline immunodeficiency and increased risk of infection. A low level of suspicion for infection should be maintained in these patients.

### 22.4.2 Endocarditis

The risk of infective endocarditis (IE) is higher in ACHD patients compared to the general population [73–78]. In a study of over 4000 ACHD patients, the incidence of IE was 3%, with the highest rates occurring in patients with unrepaired VSDs, repaired tetralogy of Fallot, and cyanotic heart disease [78]. The mortality rate of adult CHD patients with IE ranges from 4 to 8% [75]. In-hospital mortality is more likely to occur in those patients who have at least one prior cardiac surgery, patients with prosthetic material as part of their repair, patients with prior episodes of

endocarditis or an intracardiac abscess, and patients of an older age [75, 76]. A specific cause of IE is identified in only 26–30% of ACHD patients [75, 79], and only 70% of patients have an identifiable source of infection by cardiac imaging [76], likely related to difficulty visualizing the intracardiac structures due to prosthetic materials and limited acoustic windows. ACHD patients may present with heart failure, embolic phenomena, or worsening valvar dysfunction as the heralding signs of IE [76]. The presence of any of these findings with associated fevers or elevated inflammatory markers, even in the absence of an identified vegetation by imaging or positive blood cultures, should raise suspicion for endocarditis. The most common organisms that cause IE in ACHD patients mirror those in the general population: streptococci and staphylococci [76]. Patients should therefore receive broad antibiotic coverage while awaiting blood culture results and speciation of organisms. Because of the potential limitations of echocardiography, PET/CTA is an emerging diagnostic modality in patients where the diagnostic suspicion is high or the identification of the site of infection may inform the decision between medical therapy and surgical intervention [76].

### 22.4.3 Hepatitis C

Adults who underwent surgery for congenital heart defects prior to initiation of routine screening of donor blood products for hepatitis C virus (HCV) in 1992 are at risk for hepatitis C exposure. ACHD patients have higher rates of positive HCV antibody titers, suggestive of active or past infection, than the general population, ranging from 8 to 15% of those patients who underwent surgery before 1992. However, the number of patients with active infections, indicated by the presence of HCV RNA, is lower [80, 81]. Patients with more complex congenital heart lesions are more likely to have been exposed to HCV due to higher blood product exposure [80, 82, 83]. HCV screening should occur in all patients who underwent surgery prior to 1992, and for those with exposure, hepatic function should be monitored closely during their hospitalization and hepatotoxic agents should be used with caution.

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## 22.5 Integumentary and Musculoskeletal Considerations

Hospital-acquired pressure ulcers affect 3–34% of hospitalized patients [84]. Many of the risk factors for pressure ulcer development in the general adult population are frequently encountered in the ACHD population, including cardiac surgery, long hospital length of stay, long duration of mechanical ventilation, limited mobility, and infrequent repositioning. Chronic malnutrition contributes to decreased subcutaneous tissue, revealing more superficial pressure points, as well as hypoalbuminemia and poor wound healing. Use of vasoactive infusions is associated with pressure ulcer development due to the underlying low perfusion state as well as the medication-induced peripheral vasoconstriction [84]. Attention should be paid to

frequent monitoring of adult patients for ulcer development, early treatment, repositioning of immobile patients, use of pressure-alleviating mattresses and devices on pressure points, optimization of nutritional status, and frequent ambulation when the patient is able.

AChD patients are at risk for bone demineralization, increasing their risk of fracture in the ICU. In patients with PLE, the risk is likely even higher due to a combination of chronic protein losses and malnutrition, edema, treatment with medications such as heparin and steroids, and chronic use of loop diuretics, resulting in excess calcium losses [85]. Attention to positioning and fracture precautions should be employed in those patients with known significant bone demineralization. Lastly, chronic illness myopathy may be exaggerated in adults with CHD due to pre-existing malnutrition and poor muscle tone, warranting minimization of sedation when appropriate, early ambulation, and physical therapy.

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## 22.6 Endocrine

### 22.6.1 Diabetes, Insulin Resistance, and Glucose Control

Adults with CHD are at increased risk of developing type II diabetes compared to the general population (hazard ratio 1.4), and the risk is further increased in cyanotic heart disease (hazard ratio 1.9) [86]. In the ICU, improved glycemic control has been found to decrease the risk of complications in non-AChD patients. The degree of glycemic control, however, does not have to be highly intensive. The GLUCO-CABG trial [87] demonstrated no significant difference in complications between intense target glucose range of 100–140 mg/dL and a more conservative range of 141–180 mg/dL in persons undergoing coronary artery bypass surgery. Glycemic control in the ICU setting should be achieved through the use of continuous infusions of insulin allowing more nimble control of blood glucose, as hypoglycemia is associated with poor outcomes and longer hospital stays and should be treated immediately.

### 22.6.2 Thyroid Disease

Thyroid disease has an increased prevalence in trisomy 21 and 22q11 deletion syndrome. Abnormal preoperative thyroid studies are predictive of increased ICU and hospital mortality [51]. Although thyroid function screening is not routinely recommended preoperatively for patients without history of thyroid dysfunction, there should be a low threshold for screening in AChD patients with any risk factors or subclinical symptoms. Subclinical hyperthyroidism is associated with increased heart rate, atrial arrhythmias, increased left ventricular mass, impaired diastolic function, reduced exercise performance, and increased risk of cardiovascular mortality [88]. Subclinical hypothyroidism is associated with impaired systolic and diastolic function and an increased risk for atherosclerosis and myocardial infarction.

Patients with pre-existing thyroid conditions should have their thyroid status checked and medication dosages adjusted until thyroid-stimulating hormone levels are within normal limits prior to elective procedures.

Patients with moderate to severe hypothyroidism who must undergo procedures before their hypothyroidism is controlled may be at increased risk for heart failure, atrial fibrillation, and gastrointestinal and neurological complications postoperatively [89]. Those needing urgent surgery should be treated with intravenous levothyroxine prior to surgery [90]. Consider treatment with stress-dose steroids if there is concern for comorbid adrenal insufficiency.

There is a paucity of data on treatment of hyperthyroidism related to cardiac surgery. Elective surgeries should be postponed. Antithyroid medications such as thionamides (e.g., propylthiouracil and methimazole) inhibit upstream production of thyroid hormone and often take several days of treatment before having a significant clinical effect and weeks to achieve a euthyroid state. These medications should be continued postoperatively to decrease the risk of thyroid storm [91]. Beta-blockers may ameliorate many of the symptoms of hyperthyroidism in patients who require more urgent surgery. Consultation with an endocrinologist and pharmacist is recommended.

### 22.6.3 Metabolic Syndrome and Obesity

In a recent case-control study, metabolic syndrome (hypertension, hyperglycemia, excess body fat around the waist, and elevated cholesterol or triglyceride levels) was more prevalent in ACHD patients compared to controls [92]. Metabolic syndrome is associated with increased rates of adverse outcomes in both cardiac and non-cardiac surgery, including increased rates of stroke, deep vein thrombosis, acute kidney injury, wound infections, and increased length of stay [93]. Cardiac intensivists should recognize these increased risks and employ strategies outlined in the relevant sections of this chapter to ameliorate these specific risks.

Obesity is associated with increased risk for hypertension, diabetes, dyslipidemia, coronary artery disease, gall bladder disease, chronic kidney disease, restrictive lung changes, sleep apnea, and hypercapnia. A recent single-center review found comparable rates of being overweight and obese in ACHD patients with a somewhat lower rate of morbid obesity compared to control subjects [94]. Higher body mass index is associated with relatively better survival among adults with CHD, but this relationship likely reflects an association of cardiac cachexia with poor outcomes [95].

Obese persons in intensive care settings are at an increased risk of skin wounds, challenging vascular access, potentially difficult mask ventilation, and intubation [96, 97]. Ideal body weight should be considered when calculating nutritional goals. Furthermore, medications may need to be adjusted because of an increased volume of distribution for lipophilic medications, decreased proportionate lean body mass, and lower tissue water content compared to the general population [98]. Opioids should be used carefully given the risk of respiratory depression in obese patients, who already carry an increased risk of restrictive

lung disease, sleep apnea, and hypoventilation. Given differences in the relative volume of distribution, anticoagulants often warrant adjusted dosing for obese patients. Serum monitoring (e.g., anti-X<sub>a</sub> levels) for efficacy and avoidance of supra-therapeutic levels is warranted.

Ventilation strategies may require adjustment for obese patients. In contrast to nonobese persons, higher PEEP settings (10 cm H<sub>2</sub>O) were associated with improved chest wall compliance, end-expiration lung volume, and increased PaO<sub>2</sub> in morbidly obese (BMI >40) persons [99], though the effects of increased PEEP requirements in ACHD patients with passive pulmonary blood flow (e.g., Fontan circulation) or primarily right-sided heart disease must be considered.

Practical considerations regarding bed size, limits for weight of CT/MRI platforms, and the need for team lifting/lifting assist devices should be anticipated. Anticipation of these challenges is particularly important when ACHD patients are cared for in pediatric institutions.

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## 22.7 Hematology

As with all critically ill adult patients, ACHD patients admitted to an intensive care unit should be risk stratified for thrombosis and bleeding risks. All patients should receive interventions to reduce deep venous thrombosis (DVT) risk, including anti-embolism stockings, sequential compression devices, and early ambulation, unless contraindicated. These are particularly important in patients for whom pharmacologic DVT prophylaxis is contraindicated.

Certain congenital heart diseases increase the risk of thrombus formation, most notably the Fontan circulation. The Fontan circulation is associated with increased systemic venous stasis and alterations in circulating factors including decreased levels of antithrombin III, thrombomodulin, and  $\alpha$ -2-antiplasmin, lower protein C and protein S activity levels, and significantly higher levels of thrombin-antithrombin complex and  $\alpha$ 2-plasmin inhibitor complex [100]. A recent Japanese study found D-dimer was significantly elevated in patients with Fontan circulation and an intracardiac thrombus versus controls [101]. While an elevated D-dimer may prompt consideration of a CT pulmonary angiogram, CT-PA imaging is technically difficult in the Fontan circulation given increased venous transit time and often unbalanced streaming from the SVC and IVC to the right and left pulmonary arteries. A bolus of contrast from an upper extremity injection may stream into one lung. The absence of complete filling of the contralateral lung may raise concern for thrombus. An increased interval of time from contrast administration to image acquisition and/or simultaneous upper and lower limb injections may mitigate these technical issues [102].

Polycythemia is prevalent in patients with cyanosis but symptomatic hyperviscosity is uncommon. The optimal hemoglobin for a given saturation can be derived by the following equation: predicted hemoglobin =  $57.5 - (0.444 \text{ O}_{2\text{sat}})$  [103]. Patients with severe, chronic hypoxemia may have a hemoglobin concentration well above the typical index range yet be functionally anemic. If patients have a

hemoglobin significantly below their target concentration, transfusion should be considered for the symptomatic patient but must always be weighed against the risks of transfusion, including risk of sensitization to future blood products and potential need for organ transplantation. Iron deficiency should also be evaluated, as low iron levels may impair flexibility of erythrocytes. There should be a low threshold for long-term enteral iron replacement.

Hyperviscosity is a possible complication in chronic hypoxia, but it is rare below hematocrit levels of 70% [104]. Intravenous fluids should be considered if dehydration may be exacerbating the polycythemia. Phlebotomy should be reserved for symptomatic cases and only after appropriate hydration.

Thrombocytopenia is frequently observed in persons with the Fontan circulation, often attributed to hypersplenism. Given the increased risk for thrombus formation, platelet transfusion should be limited to patients with active bleeding or high risk of procedural bleeding. Neutropenia can also be observed in persons with the Fontan circulation or in patients with 22q11 microdeletion syndromes and trisomy 21.

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## 22.8 Hepatic/Gastrointestinal Disease

Chronic hepatic congestion is seen in patients with Fontan circulation. Fontan-associated liver disease (FALD) can lead to increased stiffness of the liver, portal hypertension, hypervascular liver nodules, and eventual cirrhosis. Liver dysfunction has been identified as a risk factor for perioperative mortality in adults with CHD [10]. Elevated gamma-glutamyl transferase (GGT) is the most common laboratory abnormality observed in FALD [105]. In contrast to hepatobiliary disease, alkaline phosphatase is usually not elevated to the same degree as GGT. Bilirubin, predominantly unconjugated, is most commonly normal or mildly elevated. Marked hypoalbuminemia should prompt consideration of possible PLE.

Portal hypertension increases the odds of gastrointestinal bleeding via esophageal and gastric varices and portal gastropathy. Management of gastrointestinal hemorrhage in ACHD patients is more difficult in the context of therapeutic anticoagulation or acquired coagulopathy, as seen in the setting of advanced hepatic disease. Reversal of anticoagulants and administration of clotting factors and platelets may be acutely warranted but may also increase the risk of thrombosis of prosthetic valves, mechanical support devices, systemic veins, and atrial and Fontan pathways, as well as transfusion reactions and sensitization to blood products. Given the potential for catastrophic bleeding, cardiac ICUs should have well-defined pathways for treatment of acute GI hemorrhage. This requires collaboration with gastroenterology and interventional radiology teams skilled in acute interventions such as esophageal banding. Any vascular access issues (e.g., occlusion of femoral vessels from prior catheterization/surgeries) and venous abnormalities (e.g., interrupted vena cava) should be communicated to the interventional teams in advance to avoid procedural delays and complications. Access to gastroenterologists and interventional radiologists skilled in managing acute GI hemorrhage should be taken into consideration when deciding where to care for a Fontan patient with acute GI

bleeding. This may be of particular relevance when deciding between a pediatric and adult center.

Hepatic encephalopathy has been reported in persons with the Fontan palliation [106]. While related to hyperammonemia, the relationship between ammonia level and degree of encephalopathy is neither linear nor exponential. However, extreme elevations (over 200  $\mu\text{mol}$  per liter) can lead to cerebral edema and death. The West Haven [107] and FOUR Score [108] systems can assist with the diagnosis and grading of encephalopathy. Therapies aimed at lowering the ammonia level such as lactulose remain first-line therapies.

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## 22.9 Neurologic Issues

### 22.9.1 Stroke

In a recent series, 7–9% of CHD patients suffered a stroke before age 65. Over half of adults with cyanotic CHD have evidence of prior ischemic injury on brain imaging [109]. The risk of acute thrombotic events is increased in the perioperative period and following catheter procedures. Additional risk factors include atrial arrhythmias, left-to-right shunts, and the presence of prosthetic valves. Furthermore, thrombosis of tissue valves has been increasingly recognized as a source of valve dysfunction and embolic events [110]. Infectious endocarditis can lead to embolization of infectious materials, secondary abscess formation, and vascular injury. Increasing age is also associated with atherosclerosis. Guidewires and catheters can potentially disrupt plaque and lead to an embolic event in these patients. The ICU must be vigilant for acute changes in neurological function. Focal weakness, language difficulties, and sensory impairment may more obviously raise the concern for stroke, but acute changes in level of consciousness, atypical behaviors, sudden dizziness, or changes in coordination should also be carefully evaluated.

Given the potential for significant long-term improvement with rapid reperfusion, evaluation of possible stroke must be performed in an emergent, time-efficient manner. Stroke protocols should be developed with neurology in advance to help minimize delays in diagnosis and treatment. Patients who are recovering from cardiac surgery may be ineligible for systemic thrombolytic therapy, but given advancements in catheter-based therapy, they should still be evaluated urgently by a stroke team with neuro-interventionalist involvement.

### 22.9.2 Therapeutic Hypothermia for In-Hospital Arrest

Hypothermia protocols for protection of neurologic injury in shock states are an area of active study. Studies have demonstrated a benefit for witnessed out-of-hospital ventricular fibrillation arrests in adults [111]. However, a recent observational study of adults [112] suggested harm, and a prospective trial in children [113] was stopped early due to futility. Pending more definitive prospective data in adults,

therapeutic hypothermia cannot be routinely recommended for in-hospital arrest; however, rapid rewarming for patients who are hypothermic post cardiac arrest and hyperthermia should be avoided [114].

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## 22.10 Psychosocial Concerns

### 22.10.1 Tobacco

In addition to the well-known effects of long-term smoking, nicotine withdrawal can adversely affect hospitalized patients. Nicotine withdrawal can be uncomfortable and some patients may seek to prematurely leave the hospital to smoke. Nicotine replacement therapy should be considered in patients with history of regular tobacco use. A recent meta-analysis found conflicting data about the effect of nicotine replacement therapy on agitation and delirium rates in the ICU [115]. Ideally, patients should be referred to smoking cessation programs at or prior to discharge.

### 22.10.2 Alcohol

Alcohol and/or frequent benzodiazepine use can lead to tolerance and dependency, which can occur without obvious social dysfunction. A thorough history regarding substance use is recommended, but patients may minimize or deny usage due to social stigma. Abrupt withdrawal of these agents can lead to tachycardia, agitation, hypertension, and delirium tremens. While withdrawal can begin as soon as 8 hours following the last use of alcohol, symptoms typically peak at 72 hours [116]. Symptoms may be delayed if benzodiazepines are used for sedation. Tolerance may increase sedation requirements and alternative agents should be considered. Expert consultation with anesthesiology is recommended in the acute setting and coordination with outpatient primary care and substance abuse specialists should be initiated prior to discharge.

### 22.10.3 Opiates

Opiate use and dependence are increasingly prevalent in the general population. Like patients with chronic alcohol or benzodiazepine use, opiate dependence may pose a challenge for procedural sedation. Alternative agents (e.g., propofol, ketamine, etc.) should be considered with consultation from anesthesiology. Similarly, analgesia for postoperative pain may require significant dosage adjustment and/or alternative therapies.

While postoperative pain warrants treatment, current recommendations suggest opiates should be prescribed in lower dosages and short courses with an emphasis on improving functionality rather than the elimination of discomfort. Earlier/more frequent outpatient follow-up may be warranted to help ensure that



pain is well controlled while limiting the risk of developing opiate dependence.

Intravenous and subdermal opiate use increases the risk of endocarditis and teams should be vigilant for this possibility even in the absence of an obvious usage history. Patients may also potentially abuse opiates while in the inpatient setting. ICU teams should be prepared to recognize opiate intoxications and consider it in the differential of unexplained decompensation.

#### **22.10.4 Psychiatric Care**

While there are conflicting data regarding the relative prevalence of depression among adults with congenital heart disease, recent studies from Europe have suggested rates of anxiety and depression are similar or lower in ACHD patients than in matched controls [117]. Regardless of the population-based risk, depression and anxiety can have significant implications for the perioperative patient and can be provoked by cardiac surgery [118]. Depression has been associated with increased perioperative pain in coronary artery bypass graft surgery patients [119]. Screening for depression prior to surgery may help the ICU team anticipate perioperative issues of pain control, delirium, and sleep disturbance, as well as help ensure depression is properly treated postoperatively.

Serotonin-selective reuptake inhibitors (SSRI) have been associated with increased adverse perioperative event rates [120]. It is not clear to what degree the association is causal, as much of the harm may be associated with the underlying depression or other comorbid illnesses. There is conflicting data association between SSRI use and increased perioperative bleeding, possibly due to effects on platelet aggregation, with a 2010 study of CABG patients showing no significant increased bleeding risk [121]. Typically, SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRI) are continued perioperatively as acute withdrawal can provoke flu-like symptoms, sleep disruption, altered sensation, changes in mood/thinking, and abnormal movements, including tardive dyskinesia. Given the potential for withdrawal phenomenon, stopping other medications which may have effects on platelet function such as NSAIDs should be considered first.

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### **22.11 Summary**

Adult patients with congenital heart disease are at significant risk for comorbidities in nearly every organ system. A thorough knowledge of how specific congenital cardiac physiology and interventions may predispose to comorbidities is essential for intensive care unit providers who are caring for this population of patients. Patients with palliated single-ventricle heart disease are at highest risk for comorbidities and proactive assessment of such patients may help providers avoid or minimize complications related to comorbidities. A strong working knowledge of Fontan physiology in particular will help ICU providers manage routine aspects of ICU care, such as mechanical ventilation, most effectively.

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