Heart Failure in Infants and Children
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Erin Madriago, MD,*
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Author Disclosure
Drs Madriago and Silberbach have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives After completing this article, readers should be able to:

1. Define pediatric heart failure (HF) and review its pathophysiology.
2. Describe the clinical manifestations of pediatric HF.
3. Identify common pediatric HF syndromes.
4. Recognize the differences between pediatric and adult HF.
5. Discuss the treatment of pediatric HF.

Introduction
Pediatric heart failure (HF) is an etiologically diverse disease manifesting a variety of clinical presentations. Nevertheless, in all HF syndromes, whether adult or pediatric, a unifying pathophysiologic mechanism is involved: A cardiac injury (either congenital or acquired) activates both compensatory and deleterious pathways that cause a chronic and progressive course that, if left untreated, ultimately hastens death. Indeed, pediatric HF is the most common reason that infants and children who have heart disease receive medical therapy and accounts for at least 50% of referrals for pediatric heart transplantation. (1)

Definition
HF results when cardiac output is insufficient to meet the metabolic demands of the body. Over time, decreased cardiac output leads to a cascade of compensatory responses that are aimed directly or indirectly at restoring normal perfusion to the body’s organs and tissues. For most adults, HF results from diminished myocardial contractility caused by ischemic heart disease. In contrast, decreased contractile states account for a smaller percentage of causes of pediatric HF. Instead, the various triggers of HF in children can be categorized broadly as syndromes of excessive preload, excessive afterload, abnormal rhythm, or decreased contractility, which all can lead to a final common HF pathway.

Prevalence
The overall incidence and prevalence of pediatric HF is unknown, largely because there is no accepted universal classification applied to its many forms. The largest HF burden comes from children born with congenital malformations. It has been estimated that 15% to 25% of children who have structural heart disease develop HF. (2) Although cardiomyopathy is relatively rare, approximately 40% of patients who experience cardiomyopathy develop heart failure of such severity that it leads to transplantation or death. (3)

Pathophysiology
Unmet tissue demands for cardiac output result in activation of the renin-aldosterone-angiotensin system, the sympathetic nervous system, cytokine-induced inflammation, and recently appreciated “signaling” cascades that trigger cachexia. (4) A vicious cycle begins when decreased cardiac output leads to increased metabolite production in downstream organ systems. These metabolites, in turn, stimulate local vasodilation and decreased blood pressure. Falling blood pressure stimulates angiotensin and mineralocorticoid release further, inducing fluid-retaining mechanisms in the kidney and stimulating increases in systemic vascular resis-

Abbreviations

<table>
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<tr>
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<tbody>
<tr>
<td>ANP</td>
<td>atrial natriuretic peptide</td>
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<td>BNP</td>
<td>brain natriuretic peptide</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<tr>
<td>MVO₂</td>
<td>myocardial oxygen consumption</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>tumor necrosis factor-alpha</td>
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*Division of Pediatric Cardiology, Doernbecher Children’s Hospital, Oregon Health and Science University, Portland, Ore.
Stimulation of the sympathetic nervous system and increased release of catecholamines cause tachycardia, enhanced myocardial contractility, and maladaptive forms of cardiac hypertrophy.

Initially, these effects help to improve cardiac output and maintain blood pressure. The Pediatric Advanced Life Support course offered by the American Heart Association terms this stage of HF “compensated shock.” However, HF occurs in diseases that are not readily reversible. In these situations, longstanding increases in myocardial work and myocardial oxygen consumption (MVO₂) ultimately worsen HF symptoms and lead to a chronic phase that involves cardiac remodeling (Fig. 1).

Cardiac remodeling is a structural transformation in which the normally elliptical heart increases in mass and becomes more spherical. This increase in cardiac mass (maladaptive cardiac hypertrophy) involves an expansion of the myofibril components of individual myocytes (new cells rarely form), an increase in the myocyte/capillary ratio, and activation and proliferation of abundant nonmyocyte cardiac cells, some of which produce cardiac scarring. Taken together, these processes produce a poorly contractile and less compliant heart, resulting in increased filling pressures, pulmonary or systemic edema, hypoxia, redistribution of blood flow away from skeletal muscle and the splanchnic circulation, tissue lactic acidosis, and loss of lean body mass (cachexia). Cachexia is a state of catabolic/anabolic imbalance leading to weight loss and disordered homeostasis and involves inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interleukins, as well as neurohormonal activation. Recent work suggests that activation of cachexia pathways may drive worsening HF. (5)

Although decreased cardiac output stimulates deleterious neuroendocrine mechanisms, endogenous mechanisms defend the heart from progressive HF. These mechanisms include stimulation of insulin-like growth factor and growth hormone secretion and secretion of atrial and brain natriuretic peptides (ANP and BNP). For example, growth hormone deficiency and low insulin-like growth factor concentrations have been associated with poor HF outcomes in adults, and increased concentrations appear to be protective. (6) ANP and BNP are hormones secreted by the heart in response to volume and pressure overload that increase vasodilation and diuresis acutely and chronically prevent inflammation, cardiac fibrosis, and hypertrophy. (7)

Clinical Manifestations

Because HF has multiple causes, it has a variety of age-dependent clinical presentations. In neonates, the earliest clinical manifestations may be subtle. Most commonly, infants have feeding difficulties due to dyspnea, increased fatigability, and secretion of anorexic hormones that limit the volume of feedings. Ultimately, affected babies fail to thrive. Physical findings in infants who have HF include mild-to-severe retractions, tachypnea or dyspnea with grunting (a form of positive end-expiratory pressure), tachycardia, a gallop rhythm (S₃, S₄), and hepatomegaly.

Older children manifest exercise intolerance, somnolence, anorexia, or more “adultlike” symptoms such as cough, wheezing, or crackles (rales). As with younger children, the physical examination may reveal a gallop rhythm and hepatomegaly as well as peripheral edema and jugular venous distention.

Common Causes of HF

Heart failure can result from cardiac and noncardiac causes. Cardiac causes include those associated with congenital structural malformations (Table 1) and those involving no structural anomalies (Table 2).

Cardiac Malformations Associated With Excessive Preload (Volume Loading)

Among cardiac malformations, those that cause left-to-right systolic shunts at the ventricular level are associated
most commonly with HF. In this situation, a volume load on the left side of the heart causes preload stress. The combined cardiac output is increased due to the volume of “ineffective” pulmonary blood flow that recirculates through the lungs.

Ventricular-level shunts include ventricular septal defect and patent ductus arteriosus. The left heart volume overload causes increased cardiac filling pressure and pulmonary edema. Typically, affected patients present during the first 2 to 3 postnatal months, after the natural decrease in the pulmonary vascular resistance occurs. The lower pulmonary vascular resistance relative to the systemic vascular resistance leads to a significant increase in the pulmonary blood flow relative to the systemic blood flow. Ventricular-level shunts, accordingly, have been termed “dependent” shunts because they depend on the pulmonary vascular resistance relative to the systemic vascular resistance. Excessive pulmonary venous return to the left atrium volume loads the left heart, resulting in myofiber stretching and decreased myocardial contractility.

Arteriovenous malformations divert blood from the relatively higher-resistance capillary beds of downstream tissues to low-resistance venous circuits (including the atria). These are obligate shunts. Again, the returned excessive volume leads to increased ventricular filling pressure and, ultimately, to HF.

Valvular regurgitation lesions, either acquired or congenital, also volume load the heart. These most commonly are mitral or aortic regurgitation.

Rarely, right-sided volume loading due to longstanding right ventricular preloading can lead to HF. Examples include a large atrial septal defect or anomalous pulmonary vein connections. Ventricular-level preloading also can result from congenital or surgically acquired pulmonary valve regurgitation, especially if downstream pulmonary arterial narrowing imposes an additional pressure load on the situation. Right-sided volume loading rarely causes HF early in life. Compared with the left heart, the highly compliant right ventricle accepts significant volume more readily without increasing filling pressure. Accordingly, it is only after years of volume loading that maladaptive cardiac hypertrophy occurs and patients develop HF.

Constrictive pericarditis is one of the few cardiovascular problems that can lead to HF in the setting of decreased preload. Lower cardiac filling results in decreased cardiac output. Constrictive pericarditis can result from a pericardial bacterial infection (often staphylococcal) or chest irradiation during cancer treatment, which causes fibrosis and constriction of the pericardium.
High-output HF Associated With Excessive Preload

High-output HF seen in septic shock causes a volume load on both sides of the heart and increased stroke volume associated with hyperdynamic systolic function. During sepsis, the elaboration of vasoactive molecules such as endotoxin and cytokines such as TNF-alpha leads to decreased systemic vascular resistance. Consequently, cardiac output is increased. Precapillary shunting causes decreased tissue perfusion and lactic acid production. Increased vascular permeability leads to increased total body fluid volume. In addition, toxin or direct microbial actions have negative inotropic effects. Together, these stresses produce demands for cardiac output and $MVO_2$.

Cardiac Malformations Associated With Excessive Afterload

Left heart obstructive lesions such as mitral stenosis (rare), aortic stenosis, and coarctation of the aorta (common) induce acute HF or lethal arrhythmias when they cause severe afterload stress. Affected patients often present in the first postnatal week, when the ductus arteriosus closes. In these disorders, increased end-diastolic filling pressures and a decreased pressure gradient between the aorta and ventricle at end-diastole produce subendocardial ischemia due to inadequate coronary flow. Increased afterload and subendocardial ischemia result in maladaptive cardiac hypertrophy, ventricular remodeling, and the HF syndrome.

Disorders of Contractility

Cardiomyopathy (dilated, hypertrophic, constrictive, or restrictive) is a genetically triggered or acquired disease that occurs in approximately 1.13 in 100,000 children. HF (less commonly, dysrhythmia) is the presenting feature. Different types of cardiomyopathy are illustrated in Figure 2.

Dilated cardiomyopathy is characterized by enlarged ventricular chambers and impaired systolic and diastolic function. Usually, the cause is unknown (idiopathic). Cardiomyopathy may result from infection (myocarditis), operative injury, chemotherapy (most commonly due to anthracyclines), or as a consequence of degenerative or metabolic diseases (certain muscular dystrophies, mitochondrialopathy, hyperthyroidism).

Restrictive cardiomyopathy often is idiopathic but can be caused by infiltrative or storage diseases (hemochromatosis, Pompe disease). The hallmark of restrictive cardiomyopathy is abnormal diastolic function. The echocardiographic image shows enlarged atria and non-dilated, mildly hypertrophied ventricles (a “Mickey Mouse” appearance of the heart) with abnormal tissue Doppler indices.

Hypertrophic cardiomyopathy, such as idiopathic hypertrophic subaortic stenosis, seldom is associated with pediatric HF.

Arrhythmias Associated With Pediatric HF

Arrhythmias cause HF when the heart rate is too fast or too slow to meet tissue metabolic demands. During tachycardia-related diseases, diastolic filling time shortens to the point that cardiac output is decreased. This effect can occur after several hours of significant su-
praventricular tachycardia. With chronic bradycardias, the left ventricle enlarges to accommodate larger stroke volumes. However, HF ensues when chamber dilation reaches a limit that cannot be compensated for by an increase in heart rate. Febrile states, in which metabolic demands increase rapidly, are particularly stressful in the setting of bradycardic heart diseases.

**Laboratory Studies**

Because knowledge of the specific underlying disease is critical in the understanding of the pathophysiology, management, and response to therapy for HF, certain laboratory tests are essential. Pulse oximetry is helpful in identifying cyanosis in infants who have HF caused by increased pulmonary blood flow (left-to-right shunts) because recognizing cyanosis in an infant is nearly impossible by physical examination alone. Decreased percutaneous oxygen saturation never is associated with acyanotic heart disease unless poor tissue perfusion or intrapulmonary right-to-left shunting occurs. The 12-lead electrocardiogram is essential to assess arrhythmia-induced HF. The chest radiograph may demonstrate cardiac enlargement, increased pulmonary blood flow, venous congestion, or pulmonary edema. However, chest radiographs generally have a high specificity but low sensitivity for detecting cardiac enlargement. (9) Although not useful for the evaluation of HF, which is a clinical diagnosis, echocardiography is essential for identifying causes of HF such as structural heart disease, ventricular dysfunction (both systolic and diastolic), chamber dimensions, and effusions (both pericardial and pleural).

**HF Biomarkers**

Recently, a number of HF biomarkers have been identified that aid in assessing the severity of HF and predicting the course of the disease. BNP measurement is a readily available test that can distinguish between primary respiratory disease and cardiac-induced tachypnea. (10) Because this peptide is released primarily in response to atrial stretching, it is a sensitive marker of cardiac filling pressure and diastolic dysfunction. C-reactive protein (11) and TNF-alpha (12) are both sensitive markers of systemic inflammation that correlate positively with a worse HF outcome in adult studies. C-reactive protein may augment interleukin-B, which can damage myocardium directly. TNF-alpha depresses nitric oxide endothelial relaxation acutely, an effect that can lead to ventricular remodeling and dysfunction over time. (12)

**Management**

The first goal of HF care is to treat the specific cause. Prompt treatment of noncardiac causes of HF such as anemia or endocrinopathies as well as timely referral for surgical corrections of structural cardiac anomalies can prevent or ameliorate HF. Examples include treating hypothyroidism, stopping an episode of supraventricular tachycardia, providing electronic pacing for a patient who has heart block, closing a ventricular septal defect or patent ductus arteriosus, repairing a coarctation, or relieving a valve obstruction.

HF-causing cardiac malformations usually can be approached surgically. Accordingly, medical management of HF serves as a temporizing measure if surgery must be delayed. Because there is no cure for primary childhood cardiomyopathies, the goal of medical management is to delay or eliminate the need for cardiac transplantation.

Medical therapy in children has been guided by information derived largely from studies in adults. Given the many causes of pediatric HF, it is likely that infants and children will respond differently to therapies that have been validated only in adult studies. Accordingly, it is critical that pediatric-focused trials of “standard” HF treatments be performed. Because death is a relatively rare outcome in pediatric age groups, these studies should take advantage of surrogate end points such as rate of weight gain, lengths of hospital stays, and surgical morbidities.

Medical management (Table 3) aims to maximize cardiac output and tissue perfusion while minimizing stresses that increase MVO2. These goals are accomplished by reducing the amount of force the heart needs to generate to eject blood (reducing afterload stress) and by reducing overfilling of the heart (preload). Thus, treatments that “rest” the heart, such as vasodilators, are preferred to inotropic agents that increase MVO2.

Afterload reduction is accomplished by using drugs that decrease the systemic vascular resistance. These agents include angiotensin-converting enzyme inhibitors and type 4 phosphodiesterase inhibitors (milrinone) or systemic nitrates (nitroprusside). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (losartan) also may help to inhibit cardiac fibrosis, as demonstrated in adult studies.

Another approach to resting the failing heart is through inhibition of the sympathetic nervous system. Beta-blocker therapy is a cornerstone of the medical management of HF in adults. A recent large randomized, controlled trial in children failed to show any significant improvement in clinical severity from beta-blocker therapy compared with placebo. (13) However, in that study,
the subgroup that had primarily left ventricular dysfunction had improved fraction shortening and tended to decrease their end-systolic volume in response to treatment.

Diuretics reduce preload, thereby improving Frank-Starling relationships in the heart. Decreased preload helps to prevent pulmonary edema-producing high cardiac filling pressures. Besides loop diuretics such as furosemide, other classes of diuretics are used, including thiazides and mineralocorticoid inhibitors (spironolactone). Recent data suggest that aldosterone inhibition also helps to prevent maladaptive cardiac remodeling and interstitial fibrosis.

Nesiritide, a recombinant form of BNP, promotes both diuresis and vasodilation. Nesiritide is an attractive therapy because of its multiple effects. The drug reduces both preload and afterload; directly inhibits the sympathetic nervous system, mineralocorticoid expression, and cardiac fibroblast activation; and promotes myocyte survival. Nesiritide is gaining some attention as a third-line therapy, but studies in the pediatric age group are lacking.

Digoxin is derived from the common flowering plant foxglove (Digitalis purpurea). Years ago, it was used to treat “dropsy,” renal failure, and edema. Digoxin is the only commonly used oral inotropic agent. However, its most important mechanism of action may be its ability to blunt the sympathetic nervous system, slow the heart rate, and increase cardiac filling time. Despite its wide usage in treating pediatric HF, no studies have demonstrated its efficacy. Because digoxin not only has an inotropic effect but also a chronotropic effect of slowing atrial conduction and because it is largely excreted by the kidney, its close therapeutic/toxic ratio demands close surveillance, especially if the patient is in renal failure.

Some patients who experience acute and severe unresponsive HF are treated with extracorporeal membrane oxygenation or left ventricular assist devices. These measures serve largely as bridges to transplantation but often are used to tide over the postoperative patient or the patient recovering from myocarditis, thereby obviating the need for transplantation.

The ultimate therapy for HF that is unresponsive to treatment is cardiac transplantation. The decision to proceed with heart transplantation is based on the likelihood of successful medical therapy, quality of life, donor availability, and institutional preference. Assessing disease severity is particularly problematic because of the lack of a validated, pediatric-focused HF classification system.

**Table 3. Principles of Managing Heart Failure**

<table>
<thead>
<tr>
<th>Recognition and Treatment of Underlying Systemic Disease</th>
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<tbody>
<tr>
<td>Timely Surgical Repair of Structural Anomalies</td>
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<tr>
<td>Afterload Reduction</td>
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<tr>
<td>• Angiotensin-converting enzyme inhibitors</td>
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<td>• Angiotensin receptor blockers</td>
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<tr>
<td>• Milrinone</td>
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<tr>
<td>• Nitrates</td>
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<tr>
<td>• Brain natriuretic peptide (BNP)</td>
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<tr>
<td>Preload Reduction</td>
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<tr>
<td>• Diuretics</td>
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<tr>
<td>• BNP</td>
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<tr>
<td>Sympathetic Inhibition</td>
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<tr>
<td>• Beta blockers</td>
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<tr>
<td>• BNP</td>
</tr>
<tr>
<td>• Digoxin</td>
</tr>
<tr>
<td>Cardiac Remodeling Prevention</td>
</tr>
<tr>
<td>• Mineralocorticoid inhibitors</td>
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<tr>
<td>Inotropy</td>
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<td>• Digoxin</td>
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**Prognosis**

The outcome for patients experiencing HF depends largely on its cause. When noncardiac disorders are responsible, the improvement in HF is related to successful treatment of the systemic disease. For many cardiac malformations (preload and afterload conditions), surgical correction can be curative. Unfortunately, surgery for many congenital heart lesions only palliates the underlying disease.

For example, the “unnatural” history of children who have undergone the Fontan sequence of surgical repair is development of HF for a variety of reasons. HF may occur in patients who have cardiac malformations in whom the geometrically unsuitable morphologic right ventricle generates the systemic cardiac output. One example is congenitally corrected transposition of the great vessels with ventricular inversion. In other cases, longstanding cyanosis prior to the Fontan operation may result in cardiac remodeling and maladaptive hypertrophy. In these situations, surgical management of HF is essentially palliative.

Similarly, there is no good medical approach to the
various forms of genetically triggered cardiomyopathies. Dilated cardiomyopathy commonly is treated with heart transplantation. (14) One study demonstrated that nearly 13% of patients who received new diagnoses of dilated cardiomyopathy underwent heart transplantation within 2 years of diagnosis. (8) Unfortunately, the outcomes for infants and children who have cardiomyopathy have not improved in the last 3 decades, despite technological advances in medical management and transplantation. (8) Cardiomyopathies due to metabolic or storage diseases have the worst prognoses.

In general, too little is known about HF risk assessment in children to permit confident statements about prognosis and response to treatment. The New York Heart Association Classifications, routinely used in adult studies, fail in pediatric applications because of the unique presentations of HF in children. Alternatives, such as the Ross classification (15) or the New York University Pediatric HF Index (16) also have not gained wide acceptance. A recently proposed staging system (Table 4) categorizes patients based on cause and symptoms. This system stratifies infants and children by their extent of risk at the earliest stages of heart failure and permits clinicians to discriminate between stable and decompensated disease. (17)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Interpretation</th>
<th>Clinical Examples</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>At risk for developing HF</td>
<td>Congenital heart defects, Family history of cardiomyopathy, Anthracycline exposure</td>
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<tr>
<td>B</td>
<td>Abnormal cardiac structure or function, No symptoms of HF</td>
<td>Univentricular hearts, Asymptomatic cardiomyopathy, Repaired congenital heart disease</td>
</tr>
<tr>
<td>C</td>
<td>Abnormal cardiac structure or function, Past or present symptoms of HF</td>
<td>Repaired and un-repaired congenital heart defects, Cardiomyopathies</td>
</tr>
<tr>
<td>D</td>
<td>Abnormal cardiac structure or function, Continuous infusion of intravenous inotropes or prostaglandin E1 to maintain patency of a ductus arteriosus, Mechanical ventilatory and/or mechanical circulatory support</td>
<td>Same as stage C</td>
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</table>


Table 4. Heart Failure Staging in Pediatric Heart Disease

Summary

- Based on strong research evidence, pediatric HF is a clinical syndrome that occurs when cardiac output is not sufficient to meet the metabolic demands of the body.
- Strong research evidence suggests that although there are many specific causes of HF, only a few primary mechanisms operate in all patients regardless of age (volume loading, afterload stress, disorders of rhythm, and impaired myocardial contractility). (2)
- Based on some research evidence and consensus, pediatric HF results from a less well understood set of signaling pathways that involve the sympathetic nervous system, inflammation, so-called neuroendocrine hormones, and cachexia. These pathways represent a complex interaction between maladaptive and beneficial actions.
- Based on some research evidence and consensus, the clinical presentation of HF is multifaceted and unique in children. Current medical management addresses noncardiac systemic disease and treats primary cardiac problems by surgery or medical strategies aimed at reducing preload and afterload. (21)
- The medical therapies for managing HF, including blockade of the sympathetic nervous system, afterload reduction with vasodilators, and treatment of cachexogenic pathways, were pioneered in adults and have not been well studied in children. Presently, most pediatric HF treatments depend on experience and reason rather than on evidence-based studies in infants and children.
- The validation of a pediatric system of HF classification and the acceptance of surrogate endpoints for HF studies are essential for the field to move toward reducing morbidity and mortality in children who experience HF.

References
5. von Hachling S, Doehner W, Anker SD. Nutrition, metabolism,
PIR Quiz
Quiz also available online at pedsinreview.aappublications.org.

1. The endogenous substance that best protects infants and children who have myocardial dysfunction against progressive heart failure is:
   A. Angiotensin II.
   B. Brain natriuretic peptide.
   C. Epinephrine.
   D. Interleukin-B.
   E. Tumor necrosis factor-alpha.

2. The symptom most suggestive of early heart failure in a 2-month-old infant is:
   A. Apnea.
   B. Cough.
   C. Pedal edema.
   D. Seizure.
   E. Slow feeding.

3. The primary mechanism by which an isolated ventricular septal defect produces heart failure is:
   A. Excessive afterload.
   B. Excessive preload.
   C. Impaired contractility.
   D. Impaired coronary blood flow.
   E. Induced bradydysrhythmia.

4. Which of the following assertions applies to heart failure in pediatric patients?
   A. Heart failure in most patients results from ischemic heart disease.
   B. Future improvements in treatment require a valid system for classifying the risk of heart failure.
   C. Lower concentrations of tumor necrosis factor-alpha reliably predict poorer outcomes.
   D. Recombinant brain natriuretic peptide is well established as first-line therapy.
   E. The benefits of beta-blocker therapy have been clearly demonstrated.

5. Angiotensin-converting enzyme inhibitors benefit patients who have heart failure primarily through:
   A. Afterload reduction.
   B. Inotropic effect.
   C. Preload reduction.
   D. Prevention of cardiac remodeling.
   E. Sympathetic inhibition.
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