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IN THIS ISSUE

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Neonatology Today (NT) is a monthly newsletter for Neonatologists and Perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

Upcoming Medical Meetings
(See website for additional meetings)

NeoPREP: An Intensive Review and Update of Neonatal-Perinatal Medicine
Jan. 21-27, 2012; New Orleans, LA USA
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NEO: The Conference for Neonatology
Feb. 23-26, 2012; Orlando, FL USA
www.neoconference.com

SR2.0: Speciallty Review in Neontology and Perinatology 2.0
Feb. 23-27, 2012; Orlando, FL USA
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Recruitment Ads: Pages 2 and 8

Hypoplastic Left Heart Syndrome in the Neonate

By Srilatha Alapati, MD and P. Syamasundar Rao, MD

Introduction

In the past, we discussed several general topics about Congenital Heart Disease (CHD) in the neonate,[1-5] but recently we began addressing individual cardiac lesions such as transposition of the great arteries[6] and Tetralogy of Fallot.[7] In this issue of Neonatology Today we will discuss Hypoplastic Left Heart Syndrome.

Hypoplastic Left Heart Syndrome

The term, Hypoplastic Left Heart Syndrome (HLHS), initially proposed by Noonan and Nadas,[8] describes a diminutive left ventricle with underdevelopment of mitral and aortic valves. A patent foramen ovale or an atrial septal defect is usually present. The ventricular septum is usually intact. A large patent ductus arteriosus supplies blood to the systemic circulation. Coarctation of the aorta is also commonly present.

Hypoplastic Left Heart Syndrome is a uniformly lethal cardiac abnormality unless it is surgically addressed. Since the description of surgical palliation by Norwood in the early 1980s[9,10] and the report of allograft cardiac transplantation by Bailey in the mid 1980s[11] for treatment of HLHS, the interest in this lesion has remarkably increased. The Norwood surgical approach consists of a series of three operations: Norwood procedure (Stage I), hemi-Fontan or bidirectional Glenn procedure (Stage II), and Fontan conversion (Stage III). Orthotopic heart transplantation provides an alternative therapy, with results similar to those of the staged surgical palliation. Currently, the survival rate of infants treated with these surgical approaches is similar to that of infants with other complex forms of congenital heart disease in whom a two-ventricle repair is not possible.

In this review, we will discuss anatomic, physiologic, and clinical features, noninvasive and invasive evaluation, management, and prognosis of HLHS.

Pathological Anatomy

The left ventricle is usually a thick-walled, slit-like cavity, especially when mitral atresia is present. Usually the aortic valve is severely stenosed or atretic and its annulus hypoplastic. Similarly, the mitral valve may be hypoplastic, severely stenotic or atretic. When the mitral valve is open, the left ventricular cavity is very small. Endocardial fibroelastosis is usually present. The ascending aorta is hypoplastic; its diameter may be 2 to 3 mm or less. While it is very small, it is sufficient to supply adequate coronary blood flow in a retrograde fashion. The left atrium is also small, reflecting the limited blood flow in utero. The atrial septum is usually thickened; the foramen ovale may be small and, occasionally, it may be closed. A patent ductus arteriosus is usually present and is required for survival.

A severely hypoplastic left ventricle may also be present in hearts with double-outlet right ventricle with mitral atresia, unbalanced complete atrioventricular canal and other complex heart defects; in some studies, these variants constitute as many as 25% of Hypoplastic Left Heart Syndromes patients.[12]

Pathophysiology

Prenatal Circulation

In utero, the oxygenated blood from the placenta is returned to the inferior vena cava,

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which instead of shunting across the patent foramen ovale into the left atrium mixes with the superior vena caval blood in the right atrium. The pulmonary venous blood returning into the left atrium is shunted across the atrial septum because of mitral valve obstruction. This mixed right atrial blood then crosses the tricuspid valve into the right ventricle and into the pulmonary artery.[13] Complete admixture of all venous return (that from the placenta as well as the fetus) results in blood flow with identical oxygen saturation to all parts of the fetal heart. Because of widely patent ductus arteriosus and high pulmonary vascular resistance in the fetus, most of the blood is directed into the aorta via the ductus with only a small portion of the blood from the main pulmonary artery entering the branch pulmonary arteries and lungs. Once in the aorta, the blood gets distributed into the aortic arch, brachiocephalic vessels and ascending aorta on the one hand and descending aorta on the other. The quantitative distribution into these different vascular beds depends on their relative vascular resistances. The aortic arch and ascending aortic blood flows in a reverse direction and supplies the coronary arteries.

Postnatal circulation

The newborn infant with HLHS has a complex cardiovascular physiology. Fully saturated pulmonary venous blood returning to the left atrium cannot flow into the left ventricle because of atresia, hypoplasia, or stenosis of the mitral valve. Therefore, pulmonary venous blood must cross the atrial septum (Figure 1). This blood mixes with desaturated systemic venous blood in the right atrium and from there is transmitted into the right ventricle and the pulmonary artery. The right ventricle then must pump this mixed blood to both the pulmonary and the systemic circulations that are connected in parallel, rather than in series, by the ductus arteriosus. Blood exiting the right ventricle may flow into the lungs via the branch pulmonary arteries or into the aorta via the ductus arteriosus (Figure 1). The blood flow into the aortic arch and ascending aorta is in a retrograde direction (Figure 1).

The relative flows to the pulmonary and systemic circuits depend on the relative resistances of the two vascular beds. Following birth, pulmonary vascular resistance decreases. This allows a higher percentage of the right ventricular output to go to the lungs instead of the body. Although increased pulmonary blood flow results in higher oxygen saturation, systemic blood flow is decreased. When the systemic blood flow decreases below a critical level, the perfusion becomes poor, and metabolic acidosis and oliguria may develop. There is also decreased flow to the coronary arteries and brain, with a risk of myocardial or cerebral ischemia respectively. Alternatively, if pulmonary vascular resistance is significantly higher than systemic vascular resistance, there will be hypoxemia.

In summary, the postnatal circulation in HLHS depends on three major factors:

- Adequacy of inter-atrial communication
- Patency of the ductus arteriosus
- Level of pulmonary vascular resistance

Epidemiology

Prevalence

Recently reported prevalence of HLHS varies between 0.21 and 0.28 per 1000 live births.[14] It comprises 1.2-1.5% of all congenital heart defects.[15] Hypoplastic Left Heart Syndrome accounts for 7-9% of all congenital heart disease diagnosed in the first year of life.[14,15] Before surgical treatment was available, HLHS was responsible for 25% of cardiac deaths in the neonatal period.[15] There is a higher incidence of HLHS in patients with Turner Syndrome, Noonan Syndrome, Smith-Lemli-Opitz Syndrome, and Holt-Oram Syndrome than in normal children. Certain chromosomal duplications, translocations, and deletions are also associated with HLHS.

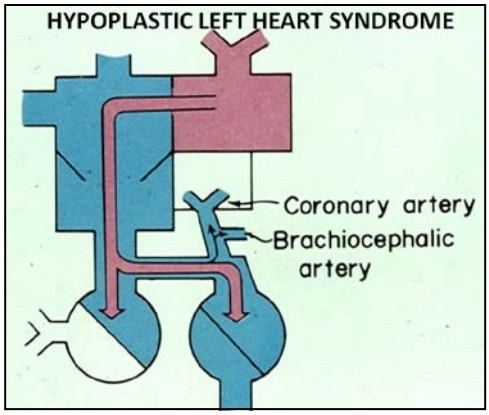

Figure 1. Box diagram of Hypoplastic Left Heart Syndrome. The pulmonary venous return cannot exit into the left ventricle and its egress has to be into the right atrium via the patent foramen ovale (PFO). Because there is no forward flow from the left heart into the hypoplastic aorta, the systemic perfusion is dependent upon the patent ductus arteriosus (PDA). Retrograde flow into the brachiocephalic vessels and coronary arteries is also shown. If the ductus constricts, the systemic perfusion is compromised. If the foramen ovale is obstructive the infant will develop signs of pulmonary venous obstruction.

Gender

The HLHS is more common in males than in females, with a 55-70% male preponderance.

Age

Babies with HLHS typically present within the first 24-48 hours of life. Presentation occurs as soon as the ductus arteriosus begins to constrict, thereby decreasing systemic blood flow, producing shock, and, without intervention, causing death. Infants with pulmonary venous obstruction (absent or restrictive patent foramen ovale) may present even sooner. Very rarely, an infant with persistence of high pulmonary vascular resistance and widely open ductus arteriosus may present later because of balanced pulmonary and systemic circulations.

Mortality/Morbidity

Without surgery, HLHS is uniformly fatal usually within the first 2 weeks of life. As alluded to above, survival for a longer period occurs rarely and is related to persistence of the ductus arteriosus along with balanced systemic and pulmonary circulations.

Following the Norwood procedure,[16] overall success (survival to hospital discharge) is approximately 75%. Success rates are higher (85%) in patients with no or a low number of preoperative risk factors and lower (45%) in patients with important and/or multiple risk factors. The risk factors for poor result include prematurity and major non-cardiac malformations. Other identified risk factors include surgery in older infants, significant tricuspid regurgitation, and pulmonary venous hypertension. High Aristotle Scores are also associated with poor prognosis.

Orthotopic heart transplantation results in early and long-term success similar to that of staged reconstruction. Among low-risk patients who undergo staged reconstruction or transplantation, actuarial survival at 5 years is approximately 70%.

Most studies report neurodevelopmental disabilities in a significant number of patients who survive either staged surgical reconstruction or cardiac transplantation.

Clinical Features

History

In the current era, most HLHS cases are diagnosed prenatally with an abnormal four-chamber view in the screening obstetric ultrasound. Prenatal diagnosis of the disease allows adequate time for parental counseling and as well as delivery planning at a tertiary care hospital, which also avoids transport-related morbidities. Following delivery, patient should be started on prostaglandin E_1 (PGE_1) to maintain ductal patency and should have an echocardiogram to confirm the diagnosis of HLHS and to assess the adequacy of the atrial septum.

In neonates with no prenatal diagnosis of HLHS, the time of presentation depends on the degree of atrial level restriction, ductal patency and the level of pulmonary vascular resistance. Most neonates are born at term and initially appear normal. As the ductus arteriosus begins to close (normally over the first 24-48 hours of life), symptoms of cyanosis, tachypnea, respiratory distress, pallor, lethargy, metabolic acidosis, and oliguria develop. Without intervention to reopen the ductus arteriosus, death rapidly ensues. Similar symptomatology may be expected if a precipitous drop in pulmonary vascular resistance occurs.

Patients with restrictive atrial level shunting (about 2-5%) can present with respiratory symptoms and profound cyanosis because of obstruction to pulmonary venous return.

Physical Examination

Before the initiation of PGE_1 infusion to reestablish patency of the ductus arteriosus, infants may exhibit signs of cardiogenic shock, including the following: hypothermia, tachycardia, respiratory distress, central cyanosis and pallor, poor peripheral perfusion with weak pulses in all extremities and in the neck and hepatosplenomegaly. After reestablishment of systemic blood flow via the ductus arteriosus, signs of shock resolve, leaving the stable infant with tachycardia, tachypnea, and mild central cyanosis. If a coarctation of the aorta is present, arterial pulses in the legs may be more prominent than those in the arms, particularly the right arm.

Findings on physical examination include prominent right ventricular impulse, normal first heart sound and a loud single second heart sound. Usually no murmur is noted; however, a nonspecific, soft, systolic ejection murmur at the left sternal border; high-pitched holosystolic murmur at the lower left sternal border, indicating tricuspid regurgitation and diastolic flow rumble over the precordium, indicating increased right ventricular diastolic filling may be heard.

Non-invasive Evaluation

Chest X-ray

The findings on chest X-ray are generally non-diagnostic but reflect the degree of atrial level shunting. With restrictive atrial shunt there will be evidence of pulmonary edema and with non-restrictive atrial level shunt there will be cardiomegaly and an increase in pulmonary vascular markings (Figure 2).

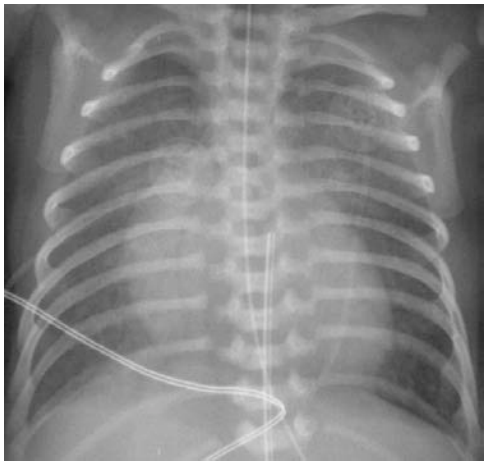

Figure 2. Chest roentgenogram in an infant with Hypoplastic Left Heart Syndrome demonstrating cardiomegaly and increased pulmonary vascular markings.

Electrocardiogram

The electrocardiogram may not be diagnostic in neonates. Right axis deviation and right ventricular hypertrophy are common, but not distinctly different from the electrocardiogram of the normal neonate. Decreased left ventricular forces are noted in the left precordial leads (Figure 3).

Echocardiogram

Echocardiography is the test of choice for diagnosing HLHS. Two dimensional imaging readily shows the hypoplastic left ventricle (Figures 4 and 5) and aorta (Figure 6) and enlarged right atrium, right ventricle (Figure 4 and 5) and main pulmonary artery. Evaluation of the aortic arch and thoracic aorta for evidence of coarctation and interruption of aortic arch is important.

Doppler and color flow Doppler are important in assessing the hemodynamics. High Doppler velocity across the atrial septum indicates restrictive inter-atrial communication (Figure 7). Doppler interrogation of the transverse arch shows retrograde systolic flow (Figure 8); this finding indicates ductal-dependent systemic circulation and supports left ventricular inadequacy for biventricular repair.

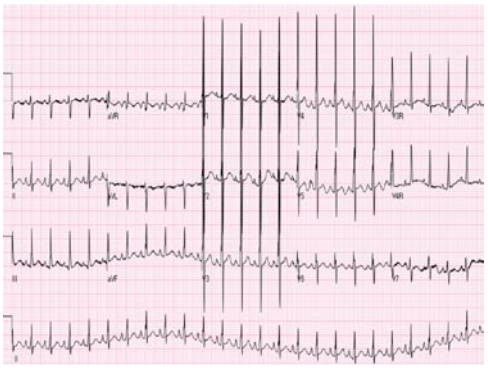

Figure 3. Electrocardiogram of an infant with Hypoplastic Left Heart Syndrome showing right axis deviation and right atrial and right ventricular hypertrophy and decreased R waves in leads V6 and V7.

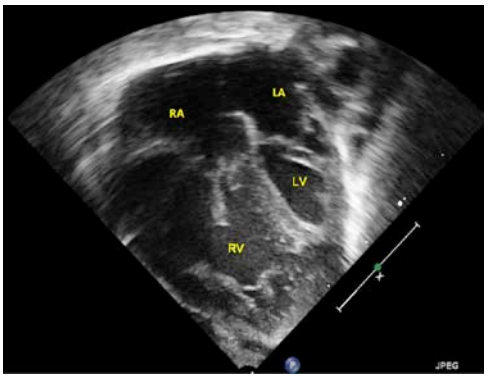

Figure 4. Two-dimensional echocardiographic apical 4-chamber view of the heart in a patient with Hypoplastic Left Heart Syndrome showing the hypoplastic left ventricle (LV), an enlarged and hypertrophied right ventricle (RV) and enlarged right atrium (RA). LA, left atrium.

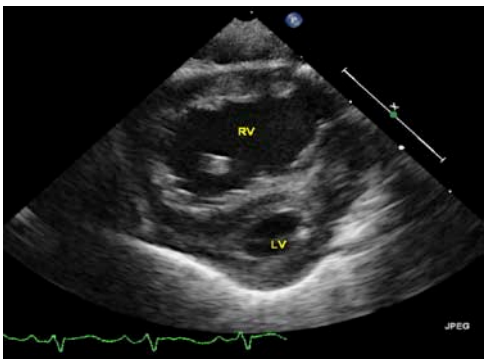

Figure 5. Two dimensional echocardiographic precordial short axis view of the heart in a patient with Hypoplastic Left Heart Syndrome demonstrating the hypoplastic left ventricle (LV) and a large right ventricle (RV).

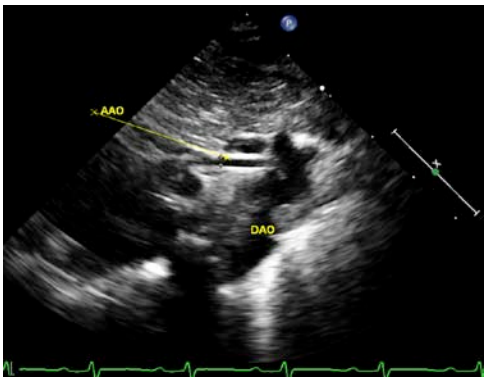

Figure 6. Two dimensional echocardiographic, supra-sternal notch, long-axis view of the aortic arch in a patient with Hypoplastic Left Heart Syndrome. This still frame shows markedly hypoplastic ascending aorta (AAO), serving only to deliver blood in a retrograde fashion to the coronary arteries. The descending aorta (DAO) is tortuous and the appearance is suggestive of aortic coarctation.

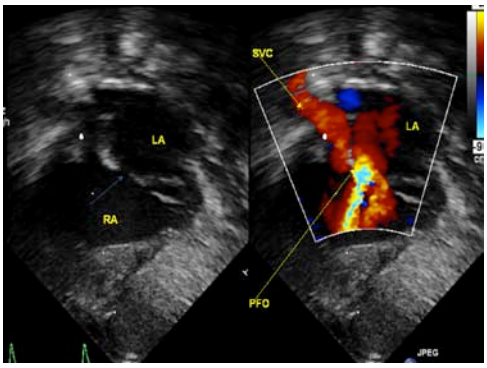

Figure 7. Subcostal views of the atrial septum in a patient with Hypoplastic Left Heart Syndrome demonstrating patent foramen ovale (blue arrow) in the left-hand panel and high velocity turbulent flow (yellow arrow) across the patent foramen ovale (PFO) in the right-hand panel. LA, left atrium; RA, right atrium; SVC, superior vena cava.

Two-dimensional and Doppler echocardiographic features are sufficiently characteristic of HLHS so that cardiac catheterization and angiography are no longer necessary for diagnosis of this anomaly.

Cardiac Catheterization and Angiography

As indicated above cardiac catheterization is rarely necessary for diagnostic purposes in the newborn period; it may be performed in cases with significantly restrictive inter-atrial communication. In these cases, transcatheter opening of the atrial septum[17,18] is undertaken to create an atrial septal defect to relieve left atrial hypertension and pulmonary edema before the Stage I surgical procedure.

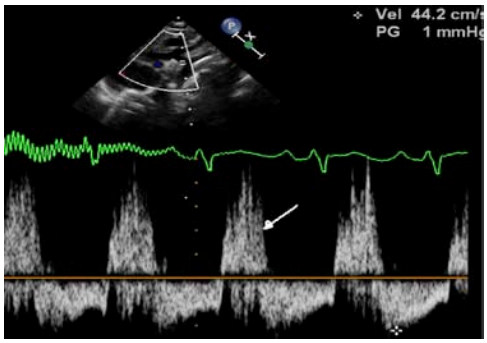

Figure 8. Doppler interrogation of the transverse arch shows retrograde systolic flow (white arrow); this finding indicates ductal-dependent systemic circulation.

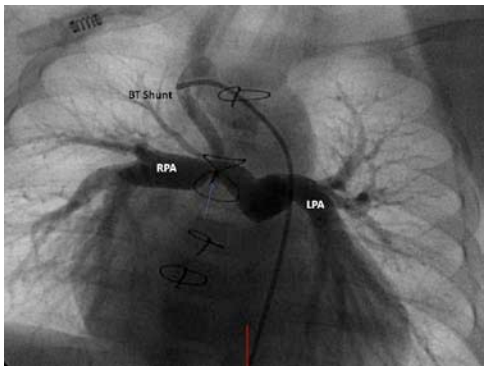

Figure 9. Selected cineangiographic frame in a left-axial oblique view of an infant with Hypoplastic Left Heart Syndrome following Norwood procedure with Blalock-Taussig (BT) shunt demonstrating good-sized right (RPA) and left (LPA) pulmonary arteries. Note moderate narrowing of the proximal RPA.

Routine catheterization at age 6 months before the bidirectional Glenn or hemi-Fontan operations, is performed to obtain hemodynamic data and calculate pulmonary vascular resistance, to evaluate the size and pressures in the pulmonary arteries and to assess the suitability of the patient for next stage procedure. Angiograms are obtained to assess the right ventricular function, tricuspid regurgitation and also to assess the branch pulmonary artery anatomy (Figures 9 and 10), and to rule out recurrent aortic coarctation and aorto-pulmonary collateral vessels. If significant collateral vessels are found, they may be occluded with coils at the same time.

Cardiac catheterization is also a standard procedure before the Fontan conversion operation. Hemodynamic data to calculate pulmonary vascular resistance and trans pulmonary gradients are obtained to assess the suitability for next stage procedure. Angiograms are obtained in similar fashion to pre-Glenn catheterization. The pulmonary artery angiograms are performed via superior vena cava (Figure 11). Coil embolization of collateral vessels is usually done at this time.

Catheter Interventions

In the neonate, obstruction at the level of patent foramen ovale is relieved by blade/balloon atrial septostomy. In cases where the blade/balloon atrial septostomy is not possible because of hypoplastic left atrium; static dilation of the atrial septum with a balloon angioplasty catheter can be done to relieve the obstruction.[17, 19]

In patients with hypoxemia due to clotted Blalock-Taussig (BT) shunts after Stage I palliation and if the patient is not ready for next stage procedure, balloon dilation or stent placement in BT shunt can be done to improve the oxygenation.[20,21] Similar interventional procedures may also become necessary in cases with obstruction of Sano shunts.

If there is recurrent aortic coarctation, balloon angioplasty may help relieve the obstruction and may help achieve reduced right ventricular afterload.[22]

If significant branch pulmonary artery stenosis or main pulmonary artery stenosis is noted before a bidirectional Glenn or Fontan conversion or after Fontan repair, pulmonary artery rehabilitation is done either by balloon angioplasty or by placement of intravascular stents.[23]

If aortopulmonary collaterals are noted, they can be occluded in the catheterization lab by coil embolization.[24]

In patients with fenestrated Fontan, the fenestration can be closed by transcatheter methods.[25,26]

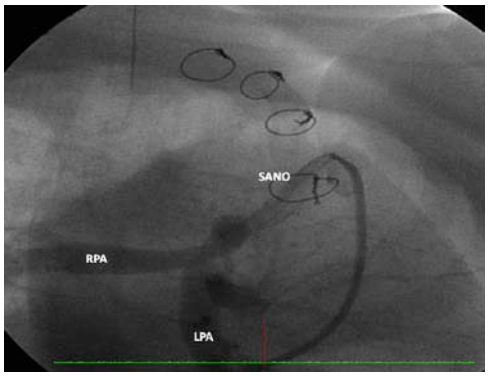

Figure 10. Selected cineangiographic frame in a right-axial oblique view of an infant with Hypoplastic Left Heart Syndrome following Norwood procedure with Sano (SANO) shunt demonstrating right (RPA) and left (LPA) pulmonary arteries.

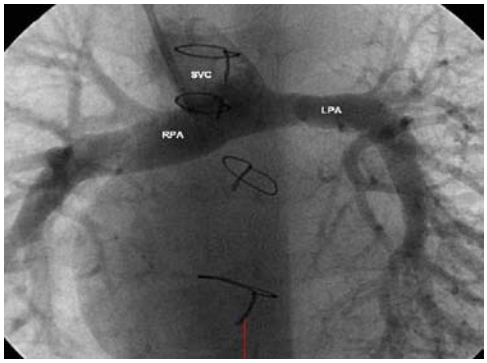

Figure 11. Selected frame from superior vena caval (SVC) cineangiogram in an infant with hypoplastic left heart syndrome following Norwood procedure with subsequent bidirectional Glenn procedure demonstrating right (RPA) and left (LPA) pulmonary arteries and no obstruction at the superior vena cava-pulmonary artery junction.

Management

A thorough explanation of different treatment approaches – supportive care, multistage surgical palliation, cardiac transplantation, including their advantages and disadvantages, should be provided to the parents.

Preoperative Medical Care

Successful preoperative management depends mainly on 3 factors:

- Providing adequate systemic flow.
- Limiting pulmonary over-circulation.
- Providing adequate egress of pulmonary venous return from the left atrium

In HLHS, the blood flow to systemic circulation (coronary arteries, brain, liver and kidneys) mainly depends on the patency of ductus arteriosus. Treatment with PGE_1 should be initiated immediately when HLHS is diagnosed or suspected to establish ductal patency and ensure adequate systemic perfusion. The patient's physiologic state often directs initial PGE_1 dosing. For patients who present in shock with suspected ductal closure or a restrictive duct, initial dose will range from 0.05 to 0.1 mcg/kg/minute. Once ductal patency is ensured, the infusion rate can be gradually decreased to an effective dose of 0.02 mcg/kg/minute. Maintaining ductal patency with the lowest effective PGE_1 dose to minimize the dose-dependent side effects of PGE_1 such as hypotension, prompting volume resuscitation and respiratory depression, requiring mechanical ventilatory support is the recommended course of action.

The pulmonary vascular resistance of a newborn is slightly less than the systemic vascular resistance and begins to fall soon after birth. In the patient with HLHS, decreased pulmonary vascular resistance (PVR) causes progressive increase in pulmonary blood flow with a concomitant decrease in systemic blood flow. When severe, this results in systemic hypo-perfusion, metabolic acidosis and shock.

After establishing ductal patency, maneuvers should be used to minimize systemic vascular resistance and maximize pulmonary vascular resistance. Importantly, maneuvers to increase PVR have been more efficacious. Intubation and mechanical ventilation with sedation and paralysis permits hypoventilation to elevate the $PaCO_2$, in the range of 45-50 mmHg. Metabolic acidosis should be corrected with sodium bicarbonate. The hematocrit should be maintained between 40–45% to provide adequate oxygen carrying capacity and to increase the blood viscosity, the latter may also serve to elevate PVR. Supplemental oxygen to increase the oxygen saturations should be avoided.

Sub-ambient oxygen (FIO_2 of 15-19%) with supplemental Nitrogen or Carbon Dioxide can be used to elevate PVR; although this is an attractive concept, it should not be pursued for long periods because severe pulmonary hypertension may complicate the postoperative course. However, this does not seem to adversely affect the pulmonary vasculature on long-term follow-up.[27]

Because of obstruction at the mitral valve, pulmonary venous blood must cross the atrial septum via a PFO and mix with desaturated systemic venous blood in the right atrium. In some patients the PFO may be restrictive. Mild restriction is acceptable and may be beneficial in that it may maintain high pulmonary vascular resistance and encourage good systemic flow. Severe restriction may cause severe hypoxemia and pulmonary edema. Periodic monitoring by echo-Doppler studies is recommended. When severe restriction develops, transcatheter interventions to enlarge the atrial septal defect may be performed. While Rashkind's balloon septostomy and Park blade septostomy are conventional methods to open atrial septum, these may not be feasible because of hypoplastic left atrium. Static dilatation of the atrial septum[17,19] with a balloon angioplasty catheter may be used which may not only relieve the obstruction, but also keep some restriction such that there is no rapid fall in the pulmonary vascular resistance. Rarely stent implantation[17] may become necessary.

Infants should remain in room air with acceptable oxygen saturation (by pulse oximetry) in the low 70s. An exceptional circumstance is the infant with severe hypoxemia caused by pulmonary venous hypertension.

Inotropic support is indicated only in severely ill neonates with concurrent sepsis or profound cardiogenic shock and acidosis. The administration of inotropes can adversely affect the balance between pulmonary and systemic vascular resistance and should be weaned off as soon as the baby is stabilized. Diuretics can be used to manage pulmonary over circulation before surgery.

It is important to recognize that the status of pulmonary vascular resistance can change rapidly, and calls for close monitoring of the patients until Norwood procedure; interventions several times a day may become necessary.

Surgical Care

The goal of surgical reconstruction of Hypoplastic Left Heart Syndrome is to eventually separate the pulmonary and systemic circulations by achieving a Fontan circulation. The right ventricle remains the systemic ventricle while blood passively flows to the lungs. This ultimate reconstruction is accomplished in the following 3 stages:

Norwood Procedure (Stage I). This procedure is usually performed during the first week of life, after the infant has been stabilized in the Neonatal Intensive Care Unit. The goals of the procedure are (1) to establish reliable systemic circulation without the ductus arteriosus and (2) to provide enough pulmonary blood flow for adequate oxygenation, while simultaneously protecting the pulmonary vascular bed in preparation for Stages II and III.

The Norwood procedure[9,10] includes (1) performing an atrial septectomy to provide unrestricted blood flow across the atrial septum, (2) ligating the ductus arteriosus, (3) creating an anastamosis between the main pulmonary artery and the aorta to provide systemic blood flow, (4) eliminating coarctation of the aorta and (5) placing an aorta–to–pulmonary artery shunt (usually a modified Blalock-Taussig shunt) to provide pulmonary circulation. More recently, connecting a Gore-Tex graft from the right ventricular outflow tract to the pulmonary artery (i.e., Sano operation) has been advocated[28,29] instead of conventional modified Blalock-Taussig shunt. The major theoretical

advantage of this arrangement is the avoidance of aorto-pulmonary runoff, which results in higher coronary and systemic perfusion pressures and may potentially lessen the incidence of ventricular ischemia. Early studies of hemodynamics documented higher diastolic coronary perfusion pressures.[29,30] However, studies comparing the two techniques among contemporary patient groups have identified no advantage of one technique over the other.[31]

Follow-up. Upon hospital discharge, most infants remain on digoxin to augment cardiac function, on diuretics to help manage right ventricular volume overload, and on aspirin to prevent thrombosis of the shunt. If tricuspid regurgitation is present, afterload reduction with Ccaptopril[10] should be used, Caution is taken in patients receiving diuretic therapy to avoid intravascular volume depletion that might reduce total cardiac output as well as increase the risk of shunt thrombosis owing to hyperviscosisty. Oxygen saturation is typically 70-80% in room air.

The incidence of inter-stage mortality is approximately 5% to 15.[32] The presence of a restrictive atrial communication, arch obstruction, obstructed shunt flow, pulmonary artery distortion, and atrio-ventricular valve insufficiency have also been associated with inter-stage mortality.[33] Commonly acquired childhood gastrointestinal or respiratory diseases that result in hypovolemia and/or acute hypoxemia have also been implicated as causes for inter-stage death.[33] After successful Stage 1 palliation, any of the above-mentioned pathologic processes can lead to increased metabolic demands and an unfavorable oxygen supply/demand relationship, placing the infant with minimal myocardial reserve at even greater risk for mortality until progression to cavopulmonary anastamosis. Therefore, transitioning infants to home after Stage 1 palliation warrants ongoing vigilance well beyond the initial early postoperative period.

Additional Surgery. Bidirectional Glenn procedure (Stage II), usually performed approximately 6 months after the Norwood procedure and Fontan procedure (Stage III), performed approximately 12 months after the bidirectional Glenn procedure will not be discussed since the current paper is focusing on neonates. Interested readers are referred to discussions presented elsewhere.[34]

Cardiac Transplantation. Heart transplantation is another surgical option.[11] The infant must remain on PGE_1 infusion to keep the ductus arteriosus patent while waiting for a donor heart to become available. Approximately 20% of infants listed for heart transplantation die while waiting for a suitable donor organ. After successful cardiac transplantation, infants require multiple medications for modulation of the immune system and prevention of graft rejection and frequent outpatient surveillance to identify rejection early and prevent lasting damage to the transplanted heart. Periodic endomyocardial biopsy is performed for more precise monitoring.

Emerging Therapies

***Hybrid Approach to Hypoplastic Left Heart Syndrome*:** Bilateral banding of the branch pulmonary arteries via median sternotomy and implanting stent in the ductus arteriosus is performed initially.[35] At the time of the second stage, aortic arch reconstruction, atrial septectomy, and bidirectional Glenn shunt are performed. This is followed by Fontan conversion. Although reduction of early mortality is theoretically feasible, larger experience with this approach than is currently available is necessary prior to general adaptation of this method of management of all HLHS patients.

Prevention by Fetal Intervention: Fetal echocardiography studies have shown development of HLHS in fetuses initially found to have severe/critical aortic stenosis. Some data suggest that fetal intervention to relieve aortic valve stenosis (by balloon aortic valvuloplasty) may promote normal development of the left ventricle.[36] Further research into this type of approach is needed.

Catheter-assisted Fontan: Konert et al. proposed a staged surgical-catheter approach;[37] they performed a modified hemi-Fontan procedure, instead of bidirectional Glenn shunt that is later completed by transcatheter methodology. This reduces the total number of operations required.

Prognosis

The survival rate of infants treated with surgical approaches (multi-stage surgical correction or cardiac transplant) is similar to that of infants with other complex forms of congenital heart disease in which a two-ventricle repair is not possible. The major mortality is at the time of Norwood, Stage I. Overall survival at hospital discharge after the Norwood procedure is nearly 75%.[38] Success rates are higher in uncomplicated cases and lower in cases in which important preoperative risk factors are present, such as: age greater than 1 month, significant preoperative tricuspid insufficiency, pulmonary venous hypertension, associated major chromosomal or non-cardiac abnormalities, prematurity and high Aristotle Scores (>20).[39] Survival after the bidirectional Glenn/hemi-Fontan and Fontan operations is nearly 90-95%. The actuarial survival rate after staged reconstruction is 70% at 5 years. Neurodevelopmental prognosis is not known; however, abnormalities are reported. Approximately 20% of infants listed for cardiac transplantation die while waiting for a donor heart. After successful transplantation, the survival rate at 5 years is approximately 80%. When the preoperative mortality is considered, the overall survival rate after cardiac transplantation is approximately 70%, or similar to the results for staged reconstruction.

Summary and Conclusions

Hypoplastic Left Heart Syndrome is a constellation of left heart anomalies including diminutive left ventricle with under development of mitral and aortic valves and a small and hypoplastic aorta. A patent foramen ovale and a patent ductus arteriosus are usually present and are required for survival. Coarctation of the aorta may also be present. Pulmonary venous blood crosses the atrial septum and mixes with systemic venous blood in the right atrium and from there is transmitted into the right ventricle and the pulmonary artery. The pulmonary and the systemic circulations are connected in parallel by the ductus arteriosus and the blood exiting the right ventricle is distributed into the lungs via the branch pulmonary arteries and into body via the ductus arteriosus. HLHS comprises 1.2-1.5% of all congenital heart defects and is uniformly lethal unless it is promptly identified, treated with PGE_1 and surgically palliated. Patients who are clinically-identified HLHS either by prenatal ultrasound or by-presention with symptoms as the ductus begins to close. The time of presentation depends on degree of atrial level obstruction, ductal patency and the level of pulmonary vascular resistance. The diagnosis can usually be made with echo-Doppler studies. The initial management of HLHS is by prompt infusion of PGE_1 to keep the ductus open. Balancing the pulmonary and systemic circulation to maintain adequate systemic perfusion and ensuring adequacy of patent foramen ovale for easy egress of left atrial blood while waiting for surgery are the next tasks. Surgical management is either by multi-stage surgical procedures, consisting of Norwood procedure (Stage I) in the neonatal period, hemi-Fontan or bidirectional Glenn procedure (Stage II) at about six months of age, and Fontan conversion (Stage III) one year later or orthotopic heart transplantation. Currently, the actuarial survival rate of infants treated with these surgical approaches is 70% at 5 years and is similar to that of infants with other complex forms of congenital heart disease in whom a two-ventricle repair is not possible.

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Corresponding Author

P. Syamasundar Rao, MD, Professor and Emeritus Chief of Pediatric Cardiology
Director, Pediatric Cardiology Fellowship Programs
University of Texas-Houston Medical School
6410 Fannin, UTPB Suite #425
Houston, TX 77030 USA
Phone: 713-500-5738
Fax: 713-500-5751
P.Syamasundar.Rao@uth.tmc.edu

Srilatha Alapati, MD
Interventional Pediatric Cardiology Fellow
University of Texas-Houston Medical School
Children's Memorial Hermann Hospital
Houston, TX USA

JANUARY MEDICAL MEETING FOCUS

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A Brief History of Xenon and Neuroprotection

By Meredith Holmes, BA and Jerold F. Lucey, MD, FAAP

Xenon and krypton were discovered by William Ramsay and his student Morris Travers in 1898.[1] Ramsey was awarded the Nobel Prize in chemistry in 1904 for his work on a new family of elements, the inert or noble gases.[1] Xenon is by far the least abundant of all the noble gases in the atmosphere, only a couple of milliliters are in an average room.[1] It is also very expensive; to fill a small balloon with xenon would currently cost about 140 dollars.[2]

Medical interest in xenon first began because of studies being done on the effect of pressure on mentation, particularly in relation to deep sea diving. Studies by Benke[3] observed the effects of air on mentation at 4 atm and noted that the effects were abolished by breathing 100% Oxygen gas. The conclusion drawn was that the 'narcotic' effects of air were due to the helium, nitrogen and argon. Lawrence et al.[4] postulated that 80% krypton at atmospheric pressure should be as potent as air at 6 atm and xenon should be equivalent in anaesthestic potency to air at 25 atm.[4] The hypothesis was tested on mice at atmospheric pressure and found that in mice exposed to 60-80% xenon, rapid onset of Central Nervous System (CNS) effects, such as ataxia, convulsive movements, and limb weakness was observed. The effects of the gas were seen within two minutes and reversed within 15 minutes after the xenon was removed. The study found that krypton was significantly less potent as an anaesthetic agent than xenon.

Interested in finding the action of anesthetics, Cullen and Gross[5] experimented with inert gases on rats, rabbits, and mice and found the effects of xenon to be the most pronounced. In 1951 the same team reported the first use of xenon for surgical anesthesia in humans.[5] The first patient was an 81-year-old male undergoing an orchidectomy, the second patient was a 38 year old female having a tubal ligation. The authors concluded that xenon was capable of producing complete anesthesia. In 1953 Pittinger et al.[6] used xenon as a primary anaesthetic in five patients all undergoing the same surgery to determine the clinicopathological effects of xenon. All patients received at least one hour of 80% xenon. There were no reported problems and they were unable to detect any changes in the patients' blood or urine biochemistry.

In 1990 two papers examined xenon's safety and efficiency and compared its haemodynamic and neurohumoral effects with nitrous oxide. In a study of Lachmann et al.[7] forty patients were randomized to receive either 70% nitrous oxide or 70% xenon in oxygen. While all the patients were paralyzed during surgery the xenon group had lower opiate requirements, less tendency to desaturation following induction and reported 'nice feelings and pleasant dreams.' Boomsma et al.[2] used an almost identical anaesthetic protocol and found less alteration of stress hormones during xenon anaesthesia than during nitrous oxide anesthesia. Both studies concluded that xenon was a slightly better anaesthetic agent. The cost of xenon was a major impediment to its widespread acceptance as a replacement for nitrous oxide.

"Medical interest in xenon first began because of studies being done on the effect of pressure on mentation, particularly in relation to deep sea diving."

The mechanism underlying the chemical activity of xenon was first discovered in 1998 by Franks et al.[8] The study found that although most general anaesthetics enhance the activity of inhibitory GABA (y-aminobutyric acid type-A) receptors, the effect of xenon on these receptors was negligible. The group proposed and conclusively found evidence that xenon powerfully inhibits the excitatory NMDA (N-methyl-D-asparate) receptor channels believed to be the target of ketamine and nitrous oxide.[8] This subtype of glutamate-activated ionotropic channels is implicated in synaptic mechanisms underlying learning, memory, and the perception of pain.

Finding the mechanism for xenon as an anesthetic led directly to the finding of the neuroprotective properties of xenon. Although glutamate is essential for normal brain function, the presence of excessive amounts of glutamate leads to cell death. The term excitotoxicity denotes the process whereby activation of glutamate receptors, especially those of the NMDA subtype, leads to excess calcium entry into cells which, in turn, triggers a biochemical cascade resulting in neuronal death.[9 10] Blocking the NMDA receptor and thereby excitotoxicity may, therefore, help to decrease brain damage and dysfunctions in central nervous system disorders.

Possible neuroprotection by and therapeutic action of xenon was first addressed by Wilhelm et al.[11] in a study which demonstrated that xenon reduces neuronal degeneration induced by intraperitoneal administration of N-methyl-DL-aspartate (NMDLA) and prevents excitotoxic neuronal death in cultured neurons. Studies showed that xenon reduces cerebral infarct volume induced by middle cerebral artery occlusion (MCAO), as well as NMDA - induced Ca 2 + influxes in cortical cultured neurons, a major critical event involved in excitotoxic neuronal death.[12] Other anesthetics with known NMDA receptor antagonist action like ketamine and nitrous oxide exhibit neurorotective properties, but xenon uniquely has not shown any co-existing neurotoxicity.[10] Xenon exerts its neuroprotective effect at sub anesthetic concentrations. This is clinically important because other anesthetics with known neuroprotective properties need to be administered at far higher concentrations to protect against ischemic brain injury in animal models.[11]

Xenon attenuates on-going neuronal injury on both in vitro and in vivo models of hypoxic-ischaemic injury when administered during and after the insult.[11] The neuroprotective efficacy of xenon could be observed when administered before an insult, referred to as preconditioning.[12] Xenon has been shown to enhance hypothermic neuroprotection. Moderate therapeutic hypothermia reduces brain injury and decreases death and/ or disability with improved intact neurology following experimental and clinical perinatal asphyxia. The frequency of death and disability still remain high in cooled infants necessitating the development of additional neuroprotective therapies.[13,14] Experiments with rats and pigs showed the combination of xenon and hypothermia administered 4 hours after hypoxic-ischemic injury provided synergistic neuroprotection in studies up to 30 days after the injury as did a study on cultured neurons injured by oxygen-glucose deprivation.[15] The mechanism for the combination of both hypothermia and xenon was proposed to be an antiapoptotic action.[15] A study by Thoresen et al.[16] combining hypothermia and 50% xenon as post hypoxic-ischemic therapy found the rats' functional improvement to last long-term, and was accompanied by greater improved histopathology than either of the therapies alone. Thoresen's studies have

"We are about to enter a new era of brain cooling plus what? Neonatologist will have many choices, perhaps too many! The average time required to plan, organize, find a sponsor and get FDA approval to carry out a large randomized control trial is over 10 years."

found that adding xenon inhalation to hypothermia doubles neuroprotection in both small and large newborn brain injury models.[17] These studies concluded that if applied to humans, sub-anesthetic concentrations of xenon in combination with mild hypothermia could provide a safe and effective therapy for perinatal asphyxia. For an organ system-based assessment of physiologic changes associated with hypothermia, as well as the effects of hypothermia on drug metabolism and clearance, see Zanelli S et al.[18]

The first baby to receive xenon gas to prevent brain injury was Riley Joyce in April of 2010 as a part of Marianne Thoresen's feasibility study "CoolXenon" at the University of Bristol.[19] By June 2010 nine infants were treated with whole body hypothermia and 50% xenon for up to 18 hours.[20] Thoresen believes that further work is needed in order to define an effective time window to start xenon with hypothermia treatment. Xenon is expensive and requires special ventilators. There are limited data on the window of opportunity for delayed treatment. Further clinical trials are in progress in England.

Comment

We are about to enter a new era of brain cooling plus what? Neonatologist will have many choices, perhaps too many! The average time required to plan, organize, find a sponsor and get FDA approval to carry out a large randomized control trial is over 10 years.

We should be very careful in selecting "what" should be added to cooling for future large trials. Xenon would by my choice at this time. The leaders in Xenon research are in England and Norway. They will soon be ready to start organizing large trials. We should consider joining them to carry out the large international trials.

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Corresponding Author

Meredith Holmes, BA
303 Wellington Dr.
Charlottesville VA 22903 USA
Tel: 434.989.6497

Holmes.mere@gmail.com

Jerold F. Lucey, MD, FAAP
Editor Emeritus, Pediatrics
Distinguished Professor of Pediatrics, 2011-14
University of Vermont
Burlington, VT 05401 USA

Medical News Products and Information

A Fetus Can Sense Mom's Psychological State

As a fetus grows, it's constantly getting messages from its mother. It's not just hearing her heartbeat and whatever music she might play to her belly; it also gets chemical signals through the placenta. A new study, which will be published in Psychological Science, a journal of the Association for *Psychological Science*, finds that this includes signals about the mother's mental state. If the mother is depressed, that affects how the baby develops after it's born.

In recent decades, researchers have found that the environment a fetus is growing up in—the mother's womb—is very important. Some effects are obvious. Smoking and drinking, for example, can be devastating. But others are subtler; studies have found that people who were born during the Dutch famine of 1944, most of whom had starving mothers, were likely to have health problems like obesity and diabetes later.

Curt A. Sandman, Elysia P. Davis, and Laura M. Glynn of the University of California-Irvine study how the mother's psychological state affects a developing fetus. For this study, they recruited pregnant women and checked them for depression before and after they gave birth. They also gave their babies tests after they were born to see how well they were developing.

They found something interesting: what mattered to the babies was if the environment was consistent before and after birth. That is, the babies who did best were those who either had mothers who were healthy both before and after birth, and those whose mothers were depressed before birth and stayed depressed afterward. What slowed the babies' development was changing conditions—a mother who went from depressed before birth to healthy after or healthy before birth to depressed after. "We must admit, the strength of this finding surprised us," Sandman says.

Now, the cynical interpretation of our results would be that if a mother is depressed before birth, you should leave her that way for the well-being of the infant. "A more reasonable approach would be, to treat women who present with prenatal depression. Sandman says. "We know how to deal with depression." The problem is, women are rarely screened for depression before birth.

In the long term, having a depressed mother could lead to neurological problems and psychiatric disorders, Sandman says. In another study, his team found that older children whose mothers were anxious during pregnancy, which often is co morbid with depression, have differences in certain brain structures. It will take studies lasting decades to figure out exactly what having a depressed mother means to a child's long-term health.

"We believe that the human fetus is an active participant in its own development and is collecting information for life after birth," Sandman says. "It's preparing for life based on messages the mom is providing."

Web-Based Training Helps Mental Health Professionals Worldwide

Over the past six years, more than 100,000 mental health professionals – an average of nearly 1,400 per month – have registered for a free online training program that teaches an innovative therapy to help children recover from post-traumatic stress caused by abuse, violence or natural disaster. TF-CBTWeb (www.tfcbt.musc.edu) was created by the Medical University of South Carolina in collaboration with the CARES (Child Abuse Research, Education and Services) Institute at the UMDNJ-School of Osteopathic Medicine. This web-based training allows mental health professionals to self-direct their training in trauma-focused cognitive based therapy (TF-CBT), a treatment approach developed by Esther Deblinger, PhD, Co-Director of the CARES Institute, in collaboration with Drs. Judith Cohen and Anthony Mannarino.

TF-CBTWeb training can usually be completed in about 10 hours. The program includes specific step-by-step instructions for each component of the therapy, streaming video demonstrations of the procedures involved and printable scripts and supplemental resources. The free training is provided as a courtesy of the CARES Institute and its partners in the project, the Medical University of South Carolina, Allegheny General Hospital and the National Child Traumatic Stress Network.

“Although we originally developed TF-CBT to help children recover from sexual abuse, we learned it could be adapted to effectively treat stress disorders caused by a range of traumas,” Deblinger said. “We created TF-CBTWeb to make this evidenced-based program available on a scale that we couldn’t possibly match through in-person training. The website enables us to extend our help to children around the world who have endured traumas or tragic circumstances.”

TF-CBTWeb has most recently become part of the regular staff training for the Victim Support Unit of the Ministry of Justice in Jamaica and is being used in similar fashion by agencies across the United States.

“Researchers in the Congo are using TF-CBT to work with that nation’s former child soldiers,” Deblinger said. “There is also ongoing NIMH-funded research in Zambia and an international TF-CBT group is forming that will include researchers and clinicians from the Netherlands, Norway, Sweden, Germany and Japan.”

The CARES Institute and its partners have developed two other websites that supplement the TF-CBTWeb training program. TF-CBT Consult (http://etl2.library.musc.edu/tf-cbt-consult/index.php) provides a searchable resource that mental health professionals can access for questions about implementing TF-CBT in everyday practice situations. CTGWeb (http://ctg.musc.edu/) expands the core program to address the unique concerns of children who experience traumatic grief.

The CARES Institute provides an array of medical and mental health services developed to meet the diagnostic and therapeutic needs of children through an individualized plan for the specific circumstances of

each child and family. The CARES Institute is a nationally recognized model of excellence in healing children and families who have experienced abuse, neglect and violence.

The University of Medicine and Dentistry of New Jersey (UMDNJ) is the nation's largest free-standing public health sciences university with more than 6,000 students on five campuses attending the state's three medical schools, its only dental school, a graduate school of biomedical sciences, a school of health related professions, a school of nursing and New Jersey's only school of public health. UMDNJ operates University Hospital, a Level I Trauma Center in Newark, and University Behavioral HealthCare, which provides a continuum of healthcare services with multiple locations throughout the state.

CDC's New Congenital Heart Defect Website

The Center for Disease Control (CDC) has a new Congenital Heart Defects website www.cdc.gov/ncbddd/heartdefects/index.html, that is research-based and user-friendly.

Some of the new features of the site include:

- Easy-to-read information on prevention, risk factors, diagnosis, and living with a congenital heart defect.
- Information about specific congenital heart defects.
- A compilation of important data and scientific publications.
- An overview of the work CDC and its partners are doing in the area of congenital heart defects.

The site also includes free patient materials.

You may also follow CDC's posting messages about congenital heart defects on CDC's Facebook page (www.facebook.com/#!/CDC)

Families Report Adverse Events in Hospitalized Children Not Tracked by Health-care Providers

Families of hospitalized children can provide valuable information about adverse events relating to their children's care that complements information documented by health care professionals, states a study published in CMAJ (Canadian Medical Association Journal).

Hospitals in Canada have instituted systems to encourage reporting of adverse events — things that may negatively affect the recovery or health of a patient — in patient care. In pediatrics, it is estimated that 1% of children in hospitals experience an adverse event and 60% of these are preventable. However, there is lower reporting of these events by health care professionals compared with those documented on charts.

Researchers from British Columbia conducted a study to determine whether an adverse event system involving families would result in a change in events reporting by health care providers. The researchers expected that reporting rates would increase and that families would provide useful information on patient safety.

The study included 544 families whose children were on an inpatient ward that provided general medical, general surgical, neurologic or neurosurgical care in British Columbia's Children's Hospital to babies, children and adolescents. Each family submitted a report and of these 544 participants, 201 (37%) noted at least one adverse event or near miss during hospitalization, for a total of 321 adverse events. Adverse events included medication problems such as a reaction or incorrect dosage, treatment complications, equipment problems and miscommunication. Most of these events — 313 out of 321 — were not reported by the hospital.

However, "the results of this study showed that the introduction of a family-initiated adverse event reporting system administered at the time of discharge from a pediatric inpatient surgical ward was not associated with a change in the rate of reporting of adverse events by health care providers," writes Dr. Jeremy Daniels, University of British Columbia, with co-authors.

Only 2.5% of the events noted by families were documented by health care providers, although "almost half of the adverse events reported by families represented valid safety concerns, not merely reports of dissatisfaction," states the authors. In 139 cases, families received apologies for these incidents.

"The initiation of [the] family-based patient safety reporting system provided new opportunities to learn and improve the safety of health care provision without an additional reporting burden for health care providers," write the authors. "Giving families the opportunity to report patient safety events did not remove the barriers to reporting by providers (time pressure, culture of blame, fear of reprisal and lack of belief in the value of reporting) but served to complement such reporting."

The authors conclude that "further research is needed to delineate how best to harness the potential of families to improve the safety of the health care system."

In a related commentary www.cmaj.ca/site/embargo/cmaj111311.pdf, Drs. Charles Vincent and Rachel Davis, Imperial Centre for Patient Safety & Service Quality, Imperial College, London, UK, state that "paying close attention to patients' and families' experience of care and their reports of safety issues may be the best early warning system we have for detecting the point at which poor care deteriorates into care that is clearly dangerous."

Imperial Centre of Patient Safety and Service Quality www.cpssq.org

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Nearly Half of Physician Practices Do Not Meet National Standards for "Medical Homes"

Many Americans do not have access to a "medical home"-a physician practice that is able to manage ongoing care for patients and coordinate care among specialists and other health care facilities, according to a University of Michigan Health System-led study.

The study revealed that nearly half (46%) of physician practices do not meet national standards to qualify as a medical home.

"Our study findings are particularly worrisome because the medical home model of care is seen as providing higher quality, more cost-efficient care" said John Hollingsworth, MD, MS, the lead author

who conducted the study as a Robert Wood Johnson Foundation Clinical Scholar at the University of Michigan. "Ideally, medical homes will help keep patients with chronic diseases from getting lost in the shuffle of our complex, fragmented health care system, yet a growing number of patients do not have access to them."

The study authors mapped physician practice data from the National Ambulatory Medical Care Survey to the National Committee on Quality Assurance's standards for medical homes. They found that larger, multi-specialty groups have a greater potential for meeting medical home standards, but nine out of 10 Americans receive health care from physicians who practice in smaller, single-specialty groups.

The 2010 Health Care Reform Law provides incentives to build medical home capacity with the goal of improving care and controlling costs. Federal support for electronic health records and higher reimbursement rates for medical homes are intended to gradually increase the number of medical homes. Yet, Hollingsworth says that current market forces could push health care practices that do not have the infrastructure to be medical homes in the opposite direction and cautions that the push toward medical homes could inadvertently cause some practices to close and further restrict access to care, especially in rural areas.

The researchers' findings also suggest that health care disparities could be exacerbated because vulnerable populations, such as patients living below the poverty level, often see doctors in practices that do not meet standards for becoming a medical home.

"Patients from the poorest neighborhoods visit practices that do not meet medical home standards at higher rates than those in the more affluent neighborhoods," says Hollingsworth, an assistant professor of urology at the U-M Medical School. "These people are already economically disadvantaged and, on top of that, they wouldn't have access to the potentially higher quality of care offered by this delivery system reform."

Hollingsworth and his coauthors urge policy-makers "to address the challenges facing smaller practices" in order to "make the benefits of medical homes more equitable and widely accessible." They suggest legislative incentives to help solo or small practices to affiliate with larger physician organizations, practice team-based care, and adopt health information technology. They also recommend initiatives that would enable regional centers to facilitate medical home reforms in less populated areas.

The study, "Adoption of Medical Home Infrastructure Among Physician Practices: Policy, Pitfalls, and Possibilities," was published online on October 18 in the journal Health Services Research. It is part of a special issue on "Bridging the Gap Between Research and Health Policy" featuring research articles from current and former Robert Wood Johnson Foundation Clinical Scholars that will be released in print in February 2012.

Additional Authors: Sanjay Saint, MD, MPH; Rodney A. Hayward, MD; of U-M and the VA Ann Arbor Healthcare System. David C. Miller, MD, MPH.; Joseph W. Sakshaug, MS; of U-M. Lingling Zhang, MA; of Harvard Business School.

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Reference: 1. Clandinin MT, Van Aerde JE, Merkel KL, et al. Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and acid. *J Pediatr*. 2005;146:461-468.

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