Neonates with complex congenital heart disease may require surgical intervention in the first few days of life. The overall operative risk has decreased to 3 to 5% in most high volume centers. Morbidity has decreased as well and equally important is the improvement in quality of life. Long term normal psychomotor development is achievable in the majority of patients and need for re-operation for residual lesions has declined. Improvement in short and long term outcomes are attributed to several factors during preoperative, perioperative, and postoperative care. While decisions may be difficult, advances in neonatal cardiac surgery has resulted in our ability to offer hope to families with a high risk newborn with complex congenital heart disease (CHD) and complicated physiology.

Preoperative Advances

Fetal Diagnosis

Prenatal diagnosis of CHD may lead to benefits in early postnatal status and outcomes in certain critical forms of CHD [1,2]. The cardiac fetal screening examination during the second-trimester scan is designed to maximize the detection of heart anomalies [3] and is usually done between 18 and 22 weeks gestational age. As a minimum, the four-chamber view and outflow tract views should be included in the screening examination [4-7]. The four-chamber view can be done in 95% to 98% of pregnancies and theoretically detects > 50% of serious cardiac malformations when performed in midgestation. The three-vessel view and three vessels and trachea view are desirable.
[8, 9]. Addition of the outflow tracts and three-vessel with trachea view increases the sensitivity to as high as 90%. Indications for fetal echocardiography include chamber asymmetry, altered cardiac axis, altered position of the fetal heart, enlarged fetal heart, fetal arrhythmia on the routine scan, maternal diabetes, congenital heart disease in the mother, assisted reproduction technology, use of drugs by the mother, autoimmune disorders in the mother, history of a sibling with a cardiac anomaly, prominent nuchal translucency or increased nuchal fold thickness, structural defect in other systems, fetal infections, and IUGR in the mid-trimester [10,11]. Earlier fetal echocardiography (< 18 weeks gestational age) may be done earlier – the indication that has yielded the greatest number of fetal cardiac diagnosis is the finding of an increased nuchal translucency [12].

The fetal echocardiogram includes detailed 2D/gray-scale imaging of all cardiovascular structures, color Doppler interrogation of all valves, veins, arteries, and atrial and ventricular septae, and assessment of cardiac rhythm and function. Additional studies that may be needed are cardiac biometry, additional pulsed Doppler measure and quantitative evaluation of cardiac function. Basic fetal biometric measurements and evaluation for presence of pleural and pericardial effusions, ascites, and integumentary edema may be assessed as well. Follow-up studies are frequently needed – fetal heart disease may progress. Advanced techniques to further evaluate the fetal cardiac structure, function, and rhythm include three-dimensional and four dimensional ultrasound, cardiovascular MRI, tissue Doppler imaging, strain and strain rate imaging, fetal electrocardiography, and fetal magnetocardiography. Assessment of extracardiac anomalies in fetuses with CHD helps with pregnancy and postnatal management. Presence may have a profound impact on neonatal care [13].

**Fetal Interventions**

Fetal therapy is indicated and available for fetal arrhythmias and cardiac lesions amenable to fetal intervention – aortic stenosis with evolving hypoplastic left heart syndrome (HLHS), HLHS with restrictive/intact atrial septum, dilated left ventricle with severe mitral regurgitation/aortic stenosis/restrictive or intact atrial septum, and pulmonary atresia/intact ventricular septum (PA/IVS). Optimal techniques for open surgical repair of CHD before birth have not been developed and appropriate candidates have not been identified. Two patients are affected, mother and fetus. The current strategies include administration of medication to the mother with transplacental transfer to the fetus, minimally invasive fetoscopic-guided techniques, and invasive open uterine fetal surgery.

Fetal arrhythmia management for fetal bradycardia and tachycardia and fetal congestive heart failure are common. With antiarrhythmics, high doses are required during the second and third trimesters because maternal circulating blood volume and renal clearance are increased. Direct treatment of the fetus by intracordial or intramus-
cular injections may more rapidly restore sinus rhythm in the hydropic fetus. Drugs that have been used for management of fetal tachycardias include digoxin, flecainide, sotalol, amiodarone, magnesium, lidocaine, propranolol, mexiletine, and dexamethasone. A pediatric cardiologist with knowledge and expertise in managing fetal arrhythmias is needed to manage these patients.

Success of fetal cardiac catheter intervention does not always translate into clinical success after birth. The natural history of the malformation is important. Severe aortic stenosis in early gestation and midgestation evolves into HLHS at birth. Fetal intervention with in utero balloon dilation of the aortic valve is done to improve left ventricular function, improve flow through the left heart, reverse the ongoing damage to the left heart structures, and to promote left heart growth [14,15]. HLHS with restrictive or intact atrial septum has a high mortality and morbidity after delivery. Opening of the atrial septum in utero using puncture and tearing with a balloon, and stent placement have been done to limit the development of pulmonary vasculopathy [16,17]. In patients with mitral valve dysplasia syndrome with mitral regurgitation and aortic stenosis, fetal intervention to open the aortic valve [18] or opening of the atrial septum [19] have been suggested. Fetal intervention in PA/IVS is more difficult than that for the aortic valve [20]. The benefit is uncertain.

### Delivery

Care of the fetus with CHD must be coordinated between obstetric, neonatal, cardiology, and cardiothoracic surgery services. The majority of newborns with CHD do not need special care at delivery. Neonatal condition and surgical outcomes, however, are improved by delivery in close proximity to a center with the resources needed to provide medical and surgical interventions for newborns with specific major cardiac defects [1,2,13]. Level of care (LOC) assignment with delivery recommendations are as follows: LOC P – CHD in which palliative care is planned – normal delivery at local hospital; LOC 1 – CHD without predicted risk of hemodynamic instability in the delivery room or first days of life – normal delivery at local hospital; LOC 2 – CHD with minimal risk of hemodynamic instability in delivery room but requiring postnatal catheterization/surgery – delivery at hospital with neonatologist and accessible cardiology consult; LOC 3 – CHD with likely hemodynamic instability in delivery room requiring immediate specialty care for stabilization – delivery at hospital that can execute rapid care including stabilizing/lifesaving procedures; LOC 4 – CHD with expected hemodynamic instability with placental separation requiring immediate catheterization and/or surgery in delivery room to improve chance of survival – cesarean section in cardiac facility with necessary specialists in the delivery room usually at 38 to 39 weeks gestation; and LOC 5 - CHD in which cardiac transplantation is planned – list after 35 weeks of gestation, cesarean section when heart
is available [21]. Elective delivery after 39 weeks gestation improve neonatal outcomes [22]. However, waiting beyond 42 weeks is detrimental [23]. The method of delivery, spontaneous vaginal delivery versus cesarean section, has not been resolved.

**Prostaglandin**

Prostaglandin E1 (PGE1) has been routinely used to maintain ductal patency in patients with CHD who are ductal dependent. The usual initial dose is around 50-100 ng/kg/minute, but apnea, respiratory distress, hypotension, fever, and diarrhea are not uncommon with this high initial PGE1 dose. Lower doses maintain adequate patent ductus arteriosus (PDA) flows in newborns with CHD and PDA-dependent pulmonary circulation and result in fewer complications. A lower initial dose of 20 ng/kg/minute and a maintenance dose of 10 ng/kg/minute has been recommended [24,25]. Long-term infusion of PGE1 before discontinuation result in side effects which are manageable [26,27]. Intravenous use has also been used to treat pulmonary arterial hypertension [28,29] and PGE1 inhalation is also associated with reduction in pulmonary arterial pressure and improvement in arterial blood oxygen levels in pediatric patients with pulmonary arterial hypertension and has been suggested as treatment for postoperative pulmonary hypertension [30].

**Nitric Oxide**

Selective pulmonary vasodilation by inhalation of nitric oxide (iNO) prompted clinical application and FDA approval of iNO for treating hypoxemia in term neonates [31]. In term and near-term neonates, iNO decreased pulmonary vascular resistance, diminished the need for extracorporeal membrane oxygenation (ECMO), and its actions are facilitated with HFOV [32]. Use as rescue therapy for the very ill ventilated preterm infant does not appear effective [33]. When used for the postoperative management of pulmonary hypertension in infants and children with CHD, there were no differences with the use of iNO as compared with control [34]. In routine cardiac surgery, postcardiotomy right ventricular dysfunction/failure in the setting of increased pulmonary vascular resistance is the most common indications for starting iNO. Clinical practice guidelines on its use have been based on small observational or single center randomized trials. The few multicenter trials have not provided strong evidence base. The high price tag associated with iNO therapy and lack of clinical evidence requires large retrospective studies as well as prospective studies [35]. Standardized initiation and weaning guidelines for iNO is successful in reducing variation in iNO use and intensive care unit utilization while maintaining quality of care [36,37]. Sildenafil may facilitate the withdrawal of iNO and prevent rebound pulmonary hypertension in patients with CHD [38].

**Hypoxic/Hypercarbic Ventilation**

Blood flow is inversely proportional to resistance – when resistance decreases, blood flow increases. Balancing of systemic and pulmonary blood flow is important in patients with ductal-dependent CHD. After birth, pul-
monary vascular resistance (PVR) decreases. Steal from the systemic circuit results and poor perfusion, metabolic acidosis, and oliguria may be clinically observed. An increase in PVR may result in hypoxemia. Adjusting the carbon dioxide (CO₂) level using mechanical ventilation and/or sedation limits pulmonary blood flow – elevated CO₂ in the range of 45-50 mm Hg increases PVR [39,40]. Lowering the CO₂ level decreases PVR. Hypoxic gas mixtures may also be used to increase PVR [41]. Addition of nitrogen gas to the inspired gas through the endotracheal tube or hood results in a < 21% gas mixture [42,43]. Higher oxygen levels decrease PVR. The use of CO₂ and hypoxic gas have been proven to be clinically helpful in optimizing shunting by increasing PVR, but their use is controversial.

**Routine Use of Pulse Oximetry**

Critical congenital heart diseases (CCHD) are potentially life-threatening cardiac abnormalities where the systemic or pulmonary circulation is dependent on a patent ductus arteriosus and include those with duct-dependent pulmonary blood flow, inter-circulatory mixing, and systemic hypoperfusion. The seven main CCHD screening targets for neonatal pulse oximetry are hypoplastic left heart syndrome, pulmonary atresia (with intact ventricular septum), Tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, and truncus arteriosus. Early diagnosis improves outcomes. Systematic review and meta-analysis of pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies revealed that the overall sensitivity was 76.5% and specificity was 99.9%. The false-positive rate was low when it was done after 24 hours from birth [44]. The American Heart Association and the American Academy of Pediatrics suggest that routine pulse oximetry done on asymptomatic newborns after 24 hours of life but before discharge may detect critical CHD, incurs very low cost, and there is a low risk of harm [45]. European studies suggest that screening is cost-effective in identifying newborns with CCHD [46,47]. Over half of babies discharged with CHD detected in the first year of life were discharged from the hospital with a normal routine neonatal examination and the 6 week exam missed one-third of the patients [48]. In many countries, births are not attended and infants are discharged within hours of birth without medical evaluation by a qualified practioner. CCHD will go undetected in this setting.

The screening study is done on the child in the well baby nursery at 24 to 48 hours of age or shortly before discharge if < 24 hours of age. The screen is done by a qualified screener using a pulse oximeter and probes calibrated for the newborn’s right hand and either foot. A negative screen is defined as an O₂ saturation ≥ 95% in the right hand or foot and ≤ 3% difference between the right hand and foot. If the O₂ saturation is 90% to < 95% in the right hand and foot or > 3% difference in saturation between the right hand and foot, the screen is repeated in 1 hour. A negative screen is again defined as an O₂ saturation ≥ 95% in the right hand or foot and ≤ 3% difference between the
right hand and foot. If the screen again shows that the O2 saturation is 90% to < 95% in the right hand and foot or > 3% difference in saturation between the right hand and foot, the screen is again repeated in 1 hour and a negative screen is again defined as an O2 saturation ≥ 95% in the right hand or foot and ≤ 3% difference between the right hand and foot. A positive screen requires further evaluation to determine if the findings are respiratory related or cardiac related.

The local situation is key. Cardiac services are standard of care in many countries and are becoming more common in developing countries. As undetected CCHD is a cause of sudden neonatal death with patients dying at home or in the emergency department [49], early detection improves the survival of neonates and infants and improves long-term quality and quantity of life for patients identified early in life. Missing the diagnosis or detecting CCHD at an advanced stage portends poor outcomes.

Implementation of the screening program in developing countries not having access to comprehensive primary healthcare services may magnify the discrepancies in management and outcomes of congenital heart disease. However, early detection may improve overall neonatal care and outcomes, provide basic medical care, and foster an independent approach to diagnosis and management of CCHD acceptable to the population served.

The Newborn Foundation is working with global health agencies, clinicians, nongovernmental organizations (NGOs) and the medtech industry to implement the BORN (Birth Oximetry Routine for Newborns) Project. The project is aligned with the World Health Organization’s Safe Childbirth Checklist and was presented at the International Conference on Birth Defects in the Developing World in 2013. The education-and-implementation model will provide clinical education, data, and a screening framework for accurate measurements of hypoxemia in newborns. The inaugural pilot project in Sichuan Province China will evaluate nearly 50,000 newborns at county and village birth facilities. In its efforts to reduce neonatal mortality and to trigger additional NGOs and international health bodies to support pulse oximetry evaluation as a standard practice for all newborns regardless of geography, the Newborn Foundation joined with the Every Newborn Action Plan (ENAP) and newborn pulse oximetry screening is being implemented in a growing number of countries around the world. Evidence shows that using pulse oximetry and having reliable oxygen sources in district and provincial hospitals in developing countries can reduce infection-related newborn death rates by as much as 35%. A growing number of countries are implementing newborn pulse oximetry screening with the goal of reducing newborn mortality throughout the world.

Implementation of newborn pulse oximetry on a worldwide level should improve referral of the high risk newborn to facilities able to evaluate and manage CCHD. Newborn screening by pulse oximetry is an invaluable tool to improve overall newborn mortality rates, diagnose
CCHD, and to help communities decide on the care patients with CCHD may need. Many of these patients may be able to undergo interventional or surgical correction of their CHD and lead a normal life and be able to contribute to their families and communities. Delay in diagnosis may result in early death or development of irreversible lung and/or cardiac disease. Early diagnosis will help the family and community make an informed decision regarding treatment of the newborn with CCHD.

**Perioperative Advances**

**Cardiopulmonary Bypass Circuit**

The ideal neonatal cardiopulmonary bypass (CPB) circuit should combine low foreign surface area with reliable mass transfer, low priming volume, and optimal hemocompatibility. Small oxygenators, reservoirs, and filters are available – total priming volume is dependent on oxygenator position, use of vacuum-assisted return, and the correct choice of diameter and length of tubing. Miniaturization of the circuit has allowed bloodless open heart surgery to be performed in selected pediatric patients [50]. However, bloodless prime does not necessarily mean bloodless CPB or bloodless open heart surgery. Small diameter arterial tubing decreases total CPB priming volume, but is associated with higher circuit pressure, higher pressure drop, and more hemodynamic energy loss across the CPB circuit [51]. Neonates operated on using the smallest circuits spent less time in the ICU and were extubated earlier than those not done on the smallest circuits [52]. Reduction in surface area and prime volume, a perfusion strategy to avoid cardiac arrest, and warm perfusion help to blunt the systemic inflammatory response of CPB. Minimizing hemodilution reduces the inflammatory response as well [53]. CPB priming with a high colloid osmotic pressures results in a lesser extent of fluid overload by the end of CPB and priming with albumin is more appropriate in neonates than priming with crystalloids [54,55]. Adding fresh frozen plasma to CPB priming decreases postoperative blood loss [56]. Use of autologous umbilical cord blood achieves adequate end-organ oxygen delivery [57]. This is rich in HbF, platelets and other cellular constituents and induces minimal immune reaction [58]. Further studies are needed before routine clinical use of autologous umbilical cord blood in the CPB circuit.

**Alpha Stat Versus pH Stat Management for Deep Hypothermic Circulatory Arrest**

Optimal acid-base management strategy during hypothermic cardiopulmonary bypass has still not been clearly defined. Hypothermia results in an alkaline shift of blood pH. With alpha-stat strategy, CO₂ is not added to maintain a normal pH. In the pH-stat strategy, 3-5% CO₂ is added to the oxygenator gas flow to maintain a temperature-corrected blood pCO₂ of 40 mmHg and a pH of 7.40. Alpha-stat management is preferred for optimal myocardial function. The pH-stat strategy may result in loss of autoregulation of the brain and lead to cerebral microem-
bolisation and intracranial hypertension [59]. In a piglet model of deep hypothermic bypass, pH-stat management increases tissue oxygenation during deep hypothermic bypass and after circulatory arrest [60]. In another piglet study, the maximal safe duration of hypothermic circulatory arrest was found to be dependent on the temperature, hematocrit, and pH management strategy with the pH-stat strategy protecting the brain more effectively than the alpha-stat strategy [61]. Clinical studies suggest that pH-stat management in the paediatric patients results in better outcomes [62-65].

**Hematocrit**

A prospective randomized trial of 2 hemodilution strategies was shut down by the Data and Safety Monitoring Board of the National Institutes of Health because of a strongly positive outcome – infants who had a mean hematocrit of 27% had better motor skills at 1 year old relative to patients with a lowest hematocrit of 21.5%. A greater percentage of patients at 1 year of age were also classified as developmentally delayed with respect to motor skills in the lower hematocrit group [66]. A randomized trial of hemodilution to a hematocrit value of 25% versus 35% during hypothermic cardiopulmonary bypass in infants undergoing 2-ventricle repairs without aortic arch obstruction had no major benefits or risks between the two groups [67]. A hematocrit of 24% or higher at the onset of low-flow cardiopulmonary bypass is associated with higher Psychomotor Development Index scores and reduced lactate levels [68]. Current recommendations are that the hematocrit not be diluted below 24% in the newborn undergoing cardiopulmonary bypass for CHD. An inverse relationship between hematocrit and cerebral blood flow velocity during deep hypothermic cardiopulmonary bypass in neonates and infants may correlate with cerebral metabolism of oxygen, oxygen use by NIRS, and long-term neurologic outcome [68]. This is being further evaluated.

**Extracorporeal Membrane Oxygenation**

The Maquet Cardiohelp System, a portable miniaturized extracorporeal membrane oxygenator system (ECMO), is the world’s smallest heart-lung support system, is fully integrated, offers simple setup and priming techniques, and provides safe and reliable support for adult patients on ECMO during interhospital patient transport as compared to the standard circuit [69-71]. The system is intended to be used to provide circulatory and/or pulmonary support during procedures requiring CPB, to provide circulatory and/or pulmonary support during procedures not requiring CPB, to be used within and outside the hospital environment, and to be used in extracorporeal circulation during CPB in cardiac surgery. ECMO settings and oxygenator performance are similar between the Cardiohelp and standard groups [72]. Use in neonates has been limited and long-term outcome studies are required. Ex utero intrapartum therapy to ECMO has been used in late-term fetuses with expected respira-
tory and/or cardiac failure at birth, but indications have not been defined and effectiveness is not clear [73]. The artificial placenta recreates the intrauterine environment with ECMO instead of mechanical ventilation. Umbilical vessels are cannulated, mechanical ventilation is not required, and a low partial pressure of oxygen is used. These are in the developmental stage and have limited clinical availability [73,74]. The Hemolung RAS for respiratory dialysis is a simple, minimally invasive technique providing extracorporeal carbon dioxide removal for patients with acute hypercapnic respiratory failure, requires low blood flow rates, and uses a small veno-venous catheter. This technology is not yet available for neonates [75].

**Berlin Heart**

Patient selection and timing for implantation of ventricular assist devices (VAD) are not well defined. A multivariable logistic regression model predicting the likelihood of death or need for mechanical circulatory support within 60 days based on listings without mechanical circulatory support for isolated pediatric heart transplant has been developed. A simplified score (PedsMCS score) to predict the need for mechanical circulatory support based on risk factors present at listing has been developed and validated. This score is determined by the patient’s clinical condition at listing and should improve clinical decision-making [76].

The Berlin Heart Investigational device exemption (IDE) trial divided study participants into 2 cohorts based on body surface area with 24 participants in each cohort. The control group was selected from the Extracorporeal Life Support Organization (ELSO) registry [77]. For children with a BSA < 0.7 m², the median duration of support was 28 days and the primary end point (time to death or weaning from the device with an unacceptable neurologic outcome) had not been reached at 174 days [78]. The U.S. Food and Drug Administration granted Humanitarian Device Exemption approval of the Berlin Heart EXCOR Pediatric VAD on December 16, 2011. For patients with a BSA <0.7, this device is currently the only option for long-term ventricular assist device support [79]. The EXCOR VAD provides circulatory support for patients as small as 2.5 kg. Neurologic complications are the major cause of mortality for infants < 5 kg [80].

Although several other devices are being developed, it will be years before the devices are tested in clinical trials. In 2004, the National Heart, Lung and Blood Institute (NHLBI) established the Pediatric Circulatory Support Program and awarded five contracts toward the development of pediatric circulatory support devices – the Pediatric Flow VAD, the PediPump, the Pediatric Cardiopulmonary Assist System, the Pediatric Jarvik 2000, and the Pediatric VAD. NHLBI subsequently established the PumpKIN (Pumps for Kids, Infants, and Neonates) program to provide financial support for preclinical testing of the most promising devices. NHLBI has made a national commitment to making pediatric-specific VADs clinically available [81,82].
Myocardial Protection

Myocardial protection requires reduction of metabolic requirements by hypothermia and/or arrest of the contractile myocardium by depolarization of the membrane potential using high potassium blood cardioplegia [83,84]. Hypothermia is the mainstay of protection – oxygen consumption is decreased by 45% and arterial oxygen saturation increases or remains the same at 32°C and no adverse effects on the organism have been detected in the absence of cardiac fibrillation [85,86]. It is not clear whether cardioplegia is superior to hypothermia alone although cardioplegia is the gold standard of myocardial protection in neonates undergoing cardiac surgery. Physiologic differences between neonatal and adult myocardium increasing ischemia tolerance include use of glucose as the preferred substrate for adenosine triphosphate production, high glycogen content, and low 5' nucleotidase. The benefit of cardioplegia over hypothermia alone is substantial with increase in temperature [87]. Warm surgery with low prime bypass and intermittent warm blood cardioplegia is an alternative to hypothermic perfusion with cold cardioplegia using a larger priming volume and a more physiologic ATP steady state is observed with intermittent warm blood cardioplegia [88,89]. For cyanotic patients, cold blood cardioplegia with a hot shot reduces metabolic injury compared with cold crystalloid cardioplegia [90]. Meta-analysis of 34 randomised trials found a lower incidence of low cardiac output syndrome and CK-MK release with blood cardioplegia when compared with asanguineous solutions in adult patients [91]. It is not clear if this is also true in neonates.

Circulatory Arrest Versus Low Flow CPB

Prolonged deep hypothermic circulatory arrest (DHCA) is associated with brain injury – the safe duration of circulatory arrest is unknown. In neonates undergoing repair of transposition of the great arteries, neonates repaired during DHCA showed significant developmental deficits at 1 year when compared with children repaired during low-flow CPB [92]. Persistent deficits in motor skills were seen at 4 years of age in these same patients [93]. Further evaluation of these data suggests that the neurologic outcomes were affected only if the duration of DHCA exceeded 41 minutes [94]. In a randomized trial of regional cerebral perfusion (RCP) versus DHCA in newborns with functional single ventricle, RCP was not associated with improved neurodevelopmental outcomes when compared with DHCA [95]. High-flow selective cerebral perfusion leads to cerebral edema with no change in metabolic rate [96]. Management of low-flow CPB is not well-defined and cerebral vascular resistance is dynamic. Changes in requirements of flow during CPB and constituents of the perfusate for neuroprotection are being evaluated.
Attenuation of Inflammatory Responses

Systemic inflammatory response syndrome (SIRS) is induced by CPB and is more pronounced in pediatric patients – pediatric patients are immunologically immature and the organs, coagulation systems, and endocrine systems are developing. Neonates have high numbers of $T_H$ cells expressing CD4 and CD8, but these cells do not produce $T_H$ specific cytokines [97,98]. Biphasic cytokine response is less than that seen in older patients after CPB [99,100]. The clinical benefits of steroids in neonates undergoing repair of CHD on CPB is unclear [101] and is being further evaluated. Opioids enhance the anti-inflammatory effect after CPB – a greater effect is seen with fentanyl compared with morphine [102]. Heparin has both proinflammatory activation of complement during CPB and anti-inflammatory effect on neutrophils [102]. Propofol, thiopental, and sufentanil affect lymphocyte function in vitro [103], but in vivo effects are not clear. The allopurinol neurocardiac protection trial in 350 neonates who had congenital heart surgery and required cardiac surgery as a newborn did not reduce the risk of death, but did provide protection in the higher-risk HLHS survivors [104]. Topiramate and caffeine are being evaluated as neuroprotective strategies during CPB in newborns.

Ultrafiltration

In newborns, hemodilution by CPB priming results in significant complications with CPB. Ultrafiltration to remove excess water has been used to counteract these adverse effects. Conventional ultrafiltration (CUF) is carried out while CPB is running and offers limited filtration efficiency. Modified ultrafiltration (MUF), performed immediately after the termination of CPB, removes excess fluid with greater efficiency than CUF. Analysis of available evidence from several randomized controlled trials and retrospective studies showed that MUF reduces excess total body water with a clinical improvement in cardiac and pulmonary function after CPB in infants and children in the postoperative period, corrects dilutional coagulopathy, and modifies the systemic inflammatory response [105]. MUF after separation from CPB improves pulmonary compliance and alveolar gas exchange, is associated with lower red blood cell transfusion, and is safe and reliable [106]. Meta-analysis of randomized controlled trials that examined clinical benefits of MUF over CUF in pediatric cardiac surgery indicated that MUF resulted in higher postbypass hematocrit levels and mean arterial blood pressure, but did not show improvement in postoperative blood loss, ventilator time, and ICU time [107]. Ultrafiltration and peritoneal dialysis are effective in removing proinflammatory interleukins and are renoprotective in newborns and infants undergoing cardiopulmonary bypass surgery [108]. Filter type is important as filtration profiles vary and impact the removal of inflammatory
mediators in pediatric heart surgery [109]. Comparison of MUF groups with non-MUF groups in which the CPB circuit is simplified will help determine if miniaturization of the circuit eliminates the need for MUF [110].

**Liothyronine**

In neonates, a reduction of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) after CPB is associated with increased morbidity, prolonged postoperative course, greater use of inotropes and diuretics, and longer time on mechanical ventilator support [111-113]. The Triiodothyronine for Infants and Children Undergoing CPB (TRICC) showed a significant reduction in time to extubation, less use of inotropic support, and better cardiac function with T3 supplementation in patients under 5 months old [114]. Young patients with complex operations and long bypass times might benefit most from T3 supplementation [115]. Use of intravenous T3 is commonly used in this patient population in the United States, but cost constraints and availability limits its use in many countries. Oral T3 (0.5 µg/kg to a maximum of 10 µg) starting on induction of anesthesia and then every 12 hours afterward prevents a decline in T3 [116]. Oral T3 is less expensive than the intravenous route, is not accompanied by rapid increase of peak serum level after intravenous administration, and maintains T3 levels in a stable manner [117]. Clinical trials are needed to further evaluate oral T3 use in neonates undergoing open heart surgery.

**Postoperative Advances**

**Management of Low Cardiac Output**

One quarter of newborns will decrease their index to < 2.0 L/min/m² after CPB. Myocardial dysfunction after CPB for congenital heart surgery has been attributed to the inflammatory response to CPB, effects of myocardial ischemia after cross-clamping, hypothermia, reperfusion injury, inadequate myocardial protection and ventriculotomy. Excluding residual disease is important. There is usually a time delay before low cardiac output syndrome is seen. In newborns undergoing the arterial switch procedure for D-TGA, the maximum decrease in cardiac index occurred 6 to 12 hours after separation from CPB in 32% of patients. This varies [118]. Anticipation of low cardiac output syndrome and preemptive intervention can reduce morbidity. Preload, afterload, myocardial contractility, heart rate and rhythm must be assessed in these patients. Preload must be optimized and ventricular responses to atrial pressure evaluated [119]. Allowance of right-to-left shunting at the atrial level may be helpful in patients with right ventricular dysfunction. Atrio-biventricular pacing may be useful. Atrio-ventricular sequential pacing is important for arrhythmias. Pharmacologic support may be needed to increase systemic vascular resistance or for afterload reduction. Prolonged high-dose epinephrine after CPB in neonates is associated with myocardial infarction and diastolic dysfunction. Effectiveness of prophylactic milrinone in preventing death or low cardiac output syn-
drome in newborns undergoing surgery for CHD is not clear. No differences have been shown between milrinone, levosimendan, or dobutamine in the immediate post-operative period [120]. An increase in cardiac index is seen in newborns treated with levosimendan after open-heart surgery when compared to milrinone, but multicenter trials are needed [121]. Nitric oxide reduces afterload on the right heart. Positive pressure ventilation decreases left ventricular afterload but also decreases preload. Negative pressure ventilation augments right heart function. Lowering of core body temperature for patients with low cardiac output states may reduce oxygen consumption and optimize oxygen delivery. Anti-inflammatory drugs are being used to prevent and protect organs from ischemic injury occurring during CPB and reperfusion injury. Mechanical support using ECMO or ventricular assist devices are used when other therapies fail [122].

**Ventilation/Extubation**

Weaning from mechanical ventilation is normally performed with pressure support ventilation (PSV) [123], but this conventional ventilation is not adequate in providing patient-ventilatory synchrony in infants [124]. Neurally adjusted ventilator assist (NAVA) improves the match between the patient’s needs and the assistance delivered by the ventilator – the pressure is proportional to the integral of the electrical activity of the diaphragm (EAdi) [125,126]. Use of EAdi to trigger the respiratory cycle and to deliver proportional assist with the patient’s neural drive on a breath-to-breath basis improves patient-ventilator synchrony. The number of asynchronies in NAVA is lower than that of pressure support ventilation [127-129]. In very low birth weight infants, NAVA allows neonates to use physiologic feedback to control ventilation [130,131]. NAVA is being used in newborns undergoing surgery for CHD for weaning. Long-term outcomes are not yet available. All mechanically ventilated patients able to sustain spontaneous assisted ventilation with an intact neural ventilator drive and who can undergo placement of a nasogastric tube may benefit from NAVA [125].

**Blood Products**

Blood product transfusion in adults is associated with increased morbidity and mortality after cardiac surgery. In pediatric patients, the amount of blood transfusion is not associated with mortality [132] but is associated with prolonged duration of mechanical ventilation and infection [132,133]. The absolute hemoglobin requiring transfusion in neonates with CHD has not been determined [132]. Predictors of blood transfusion are patient-related, procedure-related, and process-related. Neonates require a higher volume for the priming circuit [134] Coagulation studies are more likely to be abnormal in newborns with CHD and polycythemia worsens the coagulation profile [135]. Cyanotic patients with a hematocrit greater than 50% have prolonged coagulation time, a decreased level of fibrinogen, and thrombocytopenia [136] and are frequently on platelet inhibitors. Platelet count during
cardiopulmonary bypass (CPB) is the variable most significantly associated with blood loss [137]. Deep hypothermic circulatory arrest, hypothermia, hemodilution, long duration of CPB or a combination are related to postoperative bleeding [134,135,138]. Transfusion of < 48 hours old whole blood is associated with significantly less post-op blood loss than transfusion of packed red blood cells, fresh frozen plasma, and platelets in children under 2 years old who underwent complex cardiac surgery [139]. Prophylactic use of aprotinin is not associated with need for blood product transfusions and short-term outcome in neonates and infants [140]. Washing red blood cells and platelets reduces inflammatory biomarkers, number of transfusions, and donor exposures in patients under 17 years old undergoing cardiac surgery with CPB [141]. ε-Aminocaproic acid and tranexamic acid have been found to be equally effective with respect to perioperative transfusion requirements in newborns undergoing cardiac surgery [142]. Three-factor prothrombin complex concentrate exerts procoagulant activity compared with recombinant activated factor VII ex vivo and requires further clinical study [143]. Recombinant factor VIIa is efficient and safe in correcting hemostasis in children after CPB when other means fail [144]. The use of autologous umbilical cord blood for blood transfusion in neonates during open-heart surgery maintains a leftward shift of the HbO₂ dissociation curve during hypothermic CPB when compared to neonates who received HBa blood transfusion, but tissue oxygen delivery appears to be preserved [145]. Transfusion of blood products for survival, brain protection, and decreased morbidity in newborns with CHD needs prospective randomized studies. Outcomes will reflect the efficacy of the blood products in achieving physiologic goals resulting in improved survival with limited complications.

**Special Cases**

**Hypoplastic Left Heart Syndrome**

Almost 70% of patients with HLHS will survive into adulthood [146]. The role of fetal aortic balloon valvuloplasty and decompression of the left atrium in utero are not well-defined, but are being evaluated [147]. While prematurity, low birth weight, and genetic/extracardiac anomalies continue to adversely affect survival of newborns with HLHS, advances in surgical and perioperative management strategies have reduced the impact of the specific anatomies on survival [148-150]. The “classical” Norwood utilizing the Blalock-Taussig shunt results in diastolic run-off and can result in hemodynamic instability and coronary steal. Use of the right ventricle to pulmonary artery (RV-PA) conduit maintains diastolic pressure with a more stable postoperative course [151]. Improved pulmonary growth is also seen with the Norwood operation using a RV-PA nonvalved conduit [152]. An alternative initial procedure to the Norwood procedure for HLHS and its variants, the hybrid procedure, avoids circulatory arrest and shifts the major surgical stage to later
in life [145]. Mortality is low and midterm survival is good [153,154]. However, the need for catheter and/or surgical interventions and the slow growth of the branch pulmonary arteries pre-Fontan require further solutions [155]. Neurodevelopmental outcomes in these patients have improved as well and are reflective of changes in surgical techniques and perioperative management [156,157].

**Left Ventricular Outflow Tract Rehabilitation**

Single-ventricle palliation (SVP) results in 10-year survival rates ranging from 50% to 70% [158]. These patients are predisposed to protein-losing enteropathy, plastic bronchitis, thromboembolism, arrhythmias, and may need to undergo cardiac transplantation [159]. Patients with borderline left heart structures present a clinical challenge and a decision must be made regarding SVP or biventricular repair. Left ventricular salvage to maintain biventricular circulation in patients with high-risk anatomy (variants of hypoplastic left heart syndrome and Shone’s complex, coarctation with ventricular septal defect, and unbalanced atrioventricular canal defect) is dependent on the growth potential of the left heart structures if appropriate flow and loading conditions are present. Presence of mitral or aortic atresia in patients with intact ventricular septum is considered a contraindication to biventricular repair, but hypoplasia of left heart structures is not. Left heart rehabilitation may result in growth of left heart structures and permit biventricular repair. Surgical techniques include resection of endocardial fibroelastosis, mitral valvuloplasty to include division of tethering secondary or accessory chordae, separation of fused papillary muscles, chordal elongation of shortened primary chorda, commissurotomy for commissural fusion, augmentation of deficient leaflets, and debridement of thickened leaflet tissue, redistribution of atroventricular valve tissue, aortic valvuloplasty to include commissurotomy, debridement of thickened aortic valve leaflets, and augmentation of deficient leaflets, atrial septal defect restriction, transcatheter interventions, and addition of accessory pulmonary blood flow [160]. Primary left ventricular recruitment may be useful in patients with variations of Shone’s complex or borderline HLHS and surgery addresses aortic and/or mitral valve outflow tract obstruction, coarctation, and endocardial fibroelastosis [161]. Staged recruitment in patients initially considered for or who are at high risk for biventricular repair undergo SVP and simultaneous procedures to rehabilitate the left ventricle [162]. Biventricular conversion with takedown of the aortopulmonary anastomosis and re-establishment of separate left and right ventricle outflow tract continuity has been applied to patients with HLHS and unbalanced complete atrioventricular canal and borderline left heart with acceptable short-term results [163].
Tetralogy of Fallot, Pulmonary Atresia, Major Aortopulmonary Collaterals

PA/IVS with major aortopulmonary collateral arteries (MAPCAs) is a complex lesion including a tetralogy of fallot type of ventricular septal defect, atresia of the pulmonary valve, and pulmonary blood flow arising from systemic arterial collateral vessels. The natural history is poor and less than 50% of patients survive beyond 2 years old without intervention. Earlier surgery has been recommended to improve survival and outcomes and a staged procedure to increase pulmonary blood flow to stimulate growth of the pulmonary arteries followed by unifocalization has been the standard of care [164,165]. A modified Blalock-Taussig shunt has been the mainstay of palliation. Long-term outcomes using this strategy have been poor. The use of a right ventricle to pulmonary artery homograft in neonates has resulted in rapid and balanced growth of central pulmonary arteries allowing complete repair in most patients [166]. Staged repair is still required. In some patients with functional single ventricle and MAPCAs, unifocalization may increase venous flow to the pulmonary vascular bed and decrease cardiac volume load with resultant increase in life expectancy [167]. Early unifocalization of all important collaterals and early establishment of a low-pressure pulmonary arterial bed has resulted in improved outcomes and a protocol-based individualized approach is now recommended. Angiography defines the arborization of the pulmonary arteries. In those patients with MAPCAs having segmental level stenosis, staged unifocalization followed by staged intracardiac repair is recommended. Midline complete unifocalization is one if MAPCAs do not have segmental level stenosis. Simultaneous intracardiac repair is done in the newborns with low pulmonary artery pressures and staged intracardiac repair is done if pulmonary artery pressures are high [168,169].

Congenitally Corrected Transposition of the Great Arteries

Physiologic repair of congenitally corrected transposition of the great arteries (ccTGA) (atrioventricular and ventriculoarterial discordance) restores normal physiology, does not address ventriculoarterial discordance, places the morphologic right ventricle in the systemic position, and results in suboptimal long-term outcomes. Progressive deterioration of right ventricular function, tricuspid regurgitation, and the high rate of reintervention led to the concept of the anatomic repair. The latter procedure includes a venous and arterial switch and utilizes the left ventricle as the systemic ventricle. Clinical outcomes suggest that the repair is associated with a low operative mortality rate, superior survival, and lower New York Heart Association functional class [170,171]. In the double switch operation, the Mustard procedure is preferable – it conforms better to the unusual anatomy of the atrial septum, is more versatile, allows more optimal suture line placement, and has a lower incidence of reintervention and late death [172-174]. In those patients with
left ventricular outflow tract obstruction (LVOTO), the venous switch operation is performed in conjunction with a modified Rastelli procedure [171]. An unprepared left ventricle requires left ventricular training. Early pulmonary artery banding (<2 years old) followed by anatomic repair has low short-term mortality and favorable left ventricular and neoaortic valve function [175-177]. Late left ventricular dysfunction after anatomic repair of ccTGA is common and occurs most often in older patients and in those requiring pacing [178,179].

**Pulmonary Atresia with Intact Ventricular Septum**

Treatment strategies for pulmonary atresia with intact ventricular septum (PAIVS) depend on the type of atresia, right ventricular anatomy, tricuspid valve size and function, and presence or absence of right ventricle-to-coronary artery fistula. Group A patients have valvar or “membranous” atresia with a well-developed infundibulum and mild right ventricular hypoplasia. Patients are usually treated with radiofrequency valvotomy and balloon dilation and long-term outcomes are excellent. Group C patients have the most severe form of PA/IVS and the right ventricle is severely hypoplastic and heavily muscle-bound, major right ventricle-coronary artery connections with or without stenosis/interruptions are common, the tricuspid valve is usually competent and the right ventricle systolic pressure is often suprastemic. These patients have a duct dependent pulmonary circulation and a shunt is usually placed in the newborn period. These patients follow the SVP pathway. Long-term outcomes are similar to patients with tricuspid atresia. The intermediate Group B patients have borderline right ventricular size, the pulmonary atresia is of the valvar or membranous type, the infundibulum may be smaller than those in Group A, the pulmonary valve annulus may be small, there may be a fixed right ventricular outflow tract obstruction with suboptimal right ventricle decompression after an interventional procedure, major right ventricle-coronary artery connections are less common than in Group C patients but minor sinusoids are common, and varying degrees of tricuspid regurgitation is present. Individualized management is required for this group of patients and is determined by morphologic characteristics [180-182]. In these patients, right ventricular growth and function is difficult to predict. Catheter-based interventions to include the use of stiff wire, lasers, and radiofrequency and percutaneous perforation and balloon valvuoplasty rarely avoid the need for surgical therapy [183]. Classification based on the right ventricle hypoplasia (mild, moderate or severe hypoplasia of the right ventricle and its components) has been helpful in determining treatment. Management is usually staged with the initial goal of improving systemic arterial oxygenation and establishing forward flow through the right ventricle [184,185]. The hybrid procedure in patients not having major right ventricular-to-coronary artery communications allow decompression of the right ventricular outflow tract. The procedure is done
through a median sternotomy approach and needle perforation of the atretic plate and dilation of the pulmonary valve is performed. Simultaneous procedures - modified Blalock-Taussig shunt, bidirectional Glenn, etc. – may be performed and are dependent on the patient’s age, oxygen saturation, response to opening of the biventricular outflow tract, and the z-score of the tricuspid valve. All newborn patients have a modified Blalock-Taussig shunt placed at the the of the right ventricular outflow tract augmentation. Biventricular repair has been possible in greater than 80% of patients [186,187].

Summary

Complex CHD diagnosed in the fetus and newborn is now being medically and surgically managed with improved immediate and long-term outcomes. In utero interventions with the goal of preventing the more complex pathologies are still being evaluated and are not yet standard of care. Fetal diagnosis requires that the obstetrician, neonatologist, cardiologist, and cardiothoracic surgeon are involved in the care of the fetal patient before delivery and that plans are made for the best care of the newborn upon delivery. Preoperative advances have allowed for more stable newborns with complex CHD to undergo complicated procedures with good outcomes. Postoperative care has resulted in improved morbidities and reduced mortalities as well in these high risk patients.

References


5. Copel JA, Pilu G, Green J, Hobbins JC, Kleinman CS. Fetal echocardiographic screening for con-


54. Loeffelbein F, Zirell U, Benk C, Schlensak C, Dittrich S. High colloid oncotic pressure prim-


75. Hemolun RAS/ALung Technologies.

77. Extracorporeal Life Support Organization.
90. Modi P, Suleiman MS, Reeves B, Pawade A, Parry


112. Mackie AS, Booth KL, Newburger JW,


123. Esteban A, Ferguson ND, Meade MO, Fru-


135. Williams GD, Bratton SL, Ramamoorthy C. Factors associated with blood loss and blood


179. Huhta JC, Maloney JD, Ritter DG, Ilstrup DM, Feldt RH. Complete atrioventricular block in patients with atrioventricular discordance. Circu-


