

The Evolution of Pediatric Cardiac Critical Care



KEY WORDS: cardiac; congenital heart disease; pediatric intensive care unit; pediatrics

Somerville et al (1) in 1975 state, “With increasing experience, improved techniques in cardiac surgery, postoperative, anaesthetic, and nursing care, a progressively decreasing mortality should be expected.”

Dr. Somerville’s prescient remarks indeed heralded in a new era of improved outcomes for children born with congenital heart disease (CHD), as well as a new subspecialty dedicated to caring for critically ill infants and children with CHD. Indeed, the remarkable advances in cardiac critical care over the past 4+ decades have not occurred in a vacuum but have been the result of simultaneous progress in intraoperative assessment with epicardial and eventual transesophageal imaging (2), physiologic assessment at the bedside with portable echocardiography (3), cardiovascular pharmacology (4–7), mechanical ventilation (8), physiologic understanding of shunting and manipulation of flow through the patent arterial ductus and systemic shunts (9), bedside nursing care (10), interventional catheterization (11), cardiac surgical techniques (12), anesthesia (13), cardiopulmonary bypass (14), mechanical circulatory support (MCS) (15), and many others. Along with these advances came new treatment philosophies as well, specifically (1) early surgical repair of CHD, with minimization of palliative procedures in the newborn and infant (if corrective procedures are possible) (2), early investigations by echocardiography, catheterization, multimodal imaging, currently, if the postoperative course is not as expected, and (3) the necessity of a team-approach to the care of these children. In order to grasp this evolution, we highlight specific aspects of care.

THE PARTNERSHIP OF CRITICAL CARE AND SURGICAL PROCEDURES

The Evolution of the Care Strategies of Various Lesions

It is historically important to realize that in the early years of the 20th century, every child born with a congenital heart defect was destined to succumb to its effects, the only variable was timing; either hours or a handful of years. In the modern era, the partnership between surgery and cardiac critical care has resulted in dramatically improved outcomes with ICU mortality measured in single-digit percentages. This has come as the number of hospital admissions has steadily increased. There are very few areas in medicine, which have similar trajectories of success.

In order to grasp this evolution of success, an appreciation of the advancement in the care of specific lesions is helpful. The dramatic progression in the management of the patient with a functionally single ventricle (SV) has evolved

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hand in glove with new insights into the complex physiology of the heart, as well as the pulmonary and systemic circulations in these challenging patients.

Based on experimental work conducted in the 1940s and 1950s, it was demonstrated that systemic venous pressure could in the absence of pulmonary hypertension generate adequate pulmonary perfusion (Qp) (16, 17). Glenn (17) is credited with establishing the superior vena cava (SVC) to pulmonary artery (PA) shunt (Glenn shunt), which was first performed clinically in 1958. The first clinical application of complete right heart bypass was in 1955 by Hurwitt et al (18) as they constructed an atriopulmonary anastomosis (APA) in a 5-month-old patient with tricuspid atresia (TA). The patient died intraoperatively, which led Hurwitt to conclude, "Despite the initial appeal of the atriopulmonic shunt in the treatment of TA... there are several factors that suggest that the usefulness of this new procedure will probably be quite limited."

In 1968, Fontan and Baudet (19) resurrected the procedure by creating a Glenn shunt and APA in a 12-year old with TA, marked cyanosis, and polycythemia. Fontan and Baudet (19) credited Glenn's work as the conceptual basis for the procedure. Fontan and Baudet (19) viewed this procedure as physiologically corrective, with the hypertrophied right atrium and inlet and outlet valves assuming the work of a right ventricle (RV). From the very first reports, it was appreciated by Fontan and Baudet (19) that a "large amount of fluid infusion" was required due to "liquid storage" and that "respiratory assistance should be stopped early because positive pressure prevents central venous return." At around the same time, Kreutzer et al (20) in Buenos Aires, unaware of the work by Fontan and Baudet (19), performed an APA in a 4-year old with TA. They did not include the Glenn procedure (thought it unnecessary) nor did they include the inlet valve. Indeed, over the next few years, Kreutzer et al (20) became increasingly more aware of the futility of these valves, as he observed continuous venous flow into the PA throughout the cardiac cycle and the valves often deteriorated and became obstructive. By the 1980s, valves were no longer included as part of the procedure.

As the APA was being performed in more centers and being more widely applied to other SV variants, efforts were underway during the 1970s to develop surgical palliation for the hypoplastic left heart syndrome (HLHS), which was uniformly fatal during the first year

of life. In 1979, Norwood et al (21) initiated a program to evaluate the feasibility and efficacy of staged surgical management for HLHS. These efforts culminated in the Norwood procedure (NP), which, performed in the first few days of life, provided systemic perfusion (Qs) through an anastomosis between the main PA and the reconstructed ascending aorta and arch and Qp through a systemic artery to PA shunt (Blalock-Taussig shunt [BTS]). Norwood et al (21) in 1983 describe their experience with the first child in this program who ultimately underwent "physiologically corrective" surgery (i.e., APA) at the age of 16 months.

These surgical advances were made possible by the clinical application of another profoundly important discovery that contributed to the evolution of care of infants with a univentricular circulation, that is, the use of prostaglandin E1 (PGE1) to maintain ductal patency. Yabek and Mann (22) published in 1979 on the first use of PGE1 to restore Qs in a "moribund" infant with HLHS. PGE1 enabled them to resuscitate and stabilize the patient, allowing them to identify, "... a potentially treatable condition. PGE infusion is certainly not indicated when the diagnosis of HLHS is known."

The Fontan procedure underwent further modifications during the 1980s. As the Glenn shunt preceded the Fontan operation by several years, by the early 1980s, there were reports that those patients who had a Glenn shunt prior to the Fontan procedure experienced less hemodynamic instability and postoperative complications such as pleural effusions and renal dysfunction (23, 24). A staged approach to the Fontan operation, using the Glenn shunt as an intermediate step, was then proposed, which obligated only SVC flow to traverse the pulmonary circulation, while allowing time for regression of ventricular hypertrophy. This appreciation of a limited preload led to the development of an additional strategy during completion of the Fontan procedure, the creation of a small interatrial communication, and the so-called "fenestrated Fontan" (25).

From the beginning, the APA was recognized to result in atrial distension, which had been implicated as a factor contributing to atrial arrhythmias and thromboembolic complications. de Leval et al (26) demonstrated that in the APA, instead of providing useful work to support Qp, atrial contraction, through the generation of turbulent flow, resulted in net energy losses. On the basis of these findings, beginning in 1987, they modified the Fontan procedure by excluding most of the

atrium by interposing a conduit between the caval orifices with the cardiac end of the transected SVC anastomosed to the PA (26). In 1988, Marcelletti et al (27) introduced the extracardiac Fontan, where a graft is interposed between the transected inferior vena cava and the PA, thereby completely excluding the atria.

By the 1990s, an increasing number of centers were performing the NP albeit at a high mortality rate of 20–25% even at experienced centers. One factor thought to contribute to the high mortality rate was the physiology of the parallel circulations, where an elevated systemic vascular resistance (SVR) not only potentially causes stroke volume and total CO (Q_p and Q_s) to decrease but also alters unfavorably the distribution of total CO by increasing Q_p at the expense of Q_s , leading to tissue hypoxia. Initial strategies focused on limiting Q_p by manipulating pulmonary vascular resistance (PVR) using hypercapnia/acidosis or alveolar hypoxia (28). Beginning in the 1990s, investigators implemented a perioperative protocol that relied on the long-acting vasodilator phenoxybenzamine to reduce SVR in order to obtain high flow at low-pressure intra- and postoperatively in patients undergoing the NP (29). Tweddell et al (30) found those patients treated with phenoxybenzamine had a significantly lower arteriovenous oxygen content difference during the initial postoperative period than those treated with conventional therapies. In subsequent studies, those exposed to phenoxybenzamine were found to have significantly greater Q_p , Q_s , and total CO, and as a result greater systemic oxygen delivery (DO_2), and its use was identified as a factor favoring survival to the Glenn procedure (31).

Another factor thought to contribute to mortality following the NP was diastolic hypotension and compromised coronary perfusion resulting from the BTS. This notion led to the reapplication of the RV to PA conduit (RVPA), which was had been originally attempted by Norwood in 1981. Initial success was reported by Kishimoto et al (32, 33) in 1999 followed by Sano et al in 2003. The results of these publications and historically controlled case studies led to the Single-Ventricle Reconstruction Trial, a multicenter trial sponsored by the Pediatric Heart Network of The National Institutes of Health, where patients undergoing the NP were randomized to receive a BTS or RVPA conduit (34). The RVPA conduit was superior to the BTS for the primary endpoint of death or transplantation at 1 year; however, the significance was lost at longer follow-up.

These remarkable developments in the care of children with functionally SV variants were so profound that HLHS went from being uniformly fatal to short-term survival rates of 75% in the 1990s to the current rate of 90% at experienced centers (35). The impact of modifications in surgical and medical care of the patient undergoing the Fontan procedure have led to a remarkable improvement in outcomes (36). That being said, the original view of Fontan and Kirklin (37) that the APA was curative proved not to be substantiated. In 1990, Fontan and Kirklin (37) published the results of their study on outcomes of “perfect” Fontan operations conducted in Bordeaux and Birmingham through 1988 and found a premature decline in survival and functional status, leading to conclusion that the procedure was not curative but rather palliative. Despite this disappointing reality, outcomes however have continued to improve. The Mayo Clinic evaluated long-term outcomes of 1,052 patients who underwent the Fontan procedure at their institution from 1973 to 2012 according to the decade in which the procedure was conducted (36). Overall survival was significantly greater in those operated on after 1990, with 10- and 20-year survival rates some 15–20% higher.

It is likely that improved physiologic insights will continue to enhance functional status and survival in Fontan patients. The long-term implications of the elevated intravascular volume and systemic venous pressure to drive Q_p (as observed originally by Fontan) continue to be explored (38). The impact of the lack of a subpulmonic ventricle on the pulmonary vasculature is being studied and the long-term physiologic effects of impaired ventricular diastolic function in the setting of altered systemic arterial load are the subject of ongoing investigation.

What is apparent from the evolution of the care of the SV patient is that overall critical care practice is important, if not more so, compared with perfect surgical technique (39). In many ways, the SV patient serves as the litmus test for cardiac critical care practice. This leads us to explore the specific aspects of cardiac critical care in the child who has undergone any type of cardiac surgical procedure.

Cardiac Critical Care in the Postoperative Child

During the 45 operations in infants and children by Lillehei et al (40) in 1954 and 1955, children were hand-ventilated and endotracheal tubes were removed

on the table at the end of the procedure (41). Following extubation, postoperative care proceeded in the hospital ward, where children were placed in a closed oxygen tent. No invasive monitoring or arterial blood gases were undertaken, and all medications such as morphine and penicillin, were administered by intramuscular injections (41).

Surgeons rapidly recognized that the physique of a small child or baby (low functional residual capacity, elastic chest wall, and often supine position), especially after a major sternotomy and general anesthesia, led to breathing difficulties in the immediate postoperative phase. Thus, in the 1960s, a planned tracheostomy might be undertaken to aid the recovery (42). The transition to postoperative ventilators occurred in the 1970s and ventilator technology developed alongside our emerging ability to apply core physiology tenets, which are very pertinent to postoperative pediatric cardiac care today.

Twenty-first century postoperative management involves liberating the patient from the ventilator as soon as it is feasible and safe to do so. For a range of operations, albeit distributed toward lower complexity, with judicious anesthetic management, it is safe and advantageous to remove the endotracheal tube on the operating room table or early after admission to the ICU (43).

Nonetheless, the majority of children are ventilated postoperatively for an average of 2–3 days, while recovering from surgery and cardiopulmonary bypass (44), and a subset of complex patients for a longer period (45). Postoperative ventilator management carefully balances the principles of lung protection (avoidance of injurious shearing forces, high inspiratory pressures, and oxygen-free radicals), with the principles of cardiovascular physiology and heart-lung interactions, during the critical period when the goal is optimization of cardiac output. The distribution of blood flow and pressure flow relations of the whole lung described by J. B. West in the 1960s, remains vital. To address potential postoperative lability in PVR, the optimum is to avoid simultaneously atelectasis and also excessive changes in lung volume that may lead to pulmonary vasoconstriction (46). With left ventricular dysfunction, positive-pressure ventilation including noninvasive positive end-expiratory pressure contributes to reductions in left ventricular after load (46).

Evolution of Vasoactive Agents Including Prostaglandins

Until the late 1970s, in order for a child to survive, the diagnosis and treatment of critical neonatal heart disease had to occur within hours, before natural closure of the ductus arteriosus. Two major leaps forward in providing adequate time for patient assessment and planning of care and complex surgical interventions to be undertaken were as follows: in the late 1970s, synthetic prostaglandins were developed to maintain ductal patency, and in the late 1980s, the evolution in ultrasound technology and expertise enabled early and detailed detection of CHD including in utero (47, 48).

The fundamental postoperative issue of low cardiac output syndrome (LCOS) with impaired ventricular function was recognized in the 1970s (49). Studies in the 1990s demonstrated the nadir of LCOS during the first postoperative night, and LCOS remains a challenge today (50). Treatment of LCOS involves optimization of cardiac preload by administering colloid and pharmacotherapies in consideration of general principles of the Frank-Starling law and patient-specific considerations of systolic function, diastolic function, and individual hemodynamic issues.

In the 1970s to 1980s, research of pharmacodynamic responses to inotropes in infants and children indicated the immature myocardium has fewer contractile elements and, therefore, a decreased ability to increase contractility and responds poorly to standard techniques of manipulating preload (51). Postoperative inotropic support combinations of either (dopamine or epinephrine) and (nitroglycerine or nitroprusside) were used, with an awareness of reduced clearance of drugs in children with renal and hepatic impairments, as is common postoperatively (4). From 2000, there was increasing use of inodilator, and studies demonstrated that milrinone prevents LCOS (6).

Monitoring of the Child With Critical Cardiac Disease

Postoperative monitoring in the 1950s and 1960s entailed human observation of a small child within a closed oxygen tent, and then, noninvasive monitoring techniques emerged in the 1970s and 1980s as dedicated PICUs developed, and by the 1990s, standard of care included multidimensional monitors of electrocardiogram, peripheral oxygen saturation, end tidal

carbon dioxide, peripheral and central temperatures, invasive measurement of central venous, and arterial blood pressures (41, 52, 53). The value of clinical observations, an awareness for changes in value, suspicion of potential for errors, and interpretation of data by bedside health professionals remain at the heart of our practice to the present day (53).

Given the importance of cardiac output in postoperative care, current practice entails tracking of serum lactate levels and serial or continuous mixed venous oxygen saturation (SvO_2) values as a measure of global oxygen economy. By enabling the tailoring of therapy to immediate need, SvO_2 monitoring was a key contributor to improvements in survival following stage 1 operations for hypoplastic left heart since the millennium (54–56). Monitoring developments with a focus on protecting the brain have gained prominence in the recent era. Near-infrared spectroscopy (NIRS) provides a continuous evaluation of DO_2 , with a primary benefit of monitoring trends. Low cerebral NIRS oximetry has been linked to cardiovascular collapse and to acute neurologic events (57, 58). The role of other invasive modes of hemodynamic monitoring in the pediatric patient continues to be debated. Although much of the discussion becomes irrelevant due to size constraints, there continues to be a role for modalities such as the PA catheter and transpulmonary thermodilution (59).

Hematologic Considerations

Transfusion Thresholds in Cyanotic Heart Disease.

The oxygen-dissociation curve relates the PO_2 in the blood to the hemoglobin oxygen saturation and is crucial in determining DO_2 . Given the critical oxygen balance early after surgery, especially in cyanotic patients, there has long been a focus on maintenance of a sufficient hemoglobin level to provide adequate tissue DO_2 . Equally, there has been a developing awareness as to the hazards of transfusion, which can be infective, inflammatory, and, at excessive levels, hyperviscous. In the last 10–15 years, it has been noted that a restrictive transfusion strategy is safe when compared with a liberal transfusion strategy, supporting this approach in biventricular patients (60). The recent “Transfusion and Anaemia Expertise Initiative” (TAXI) 2018 recommended that prior to red cell transfusion, there should be consideration of risks and benefits and optimization of all physiologic contributors to DO_2 (61). In cyanotic

neonates, TAXI proposed that “solely haemoglobin based transfusion” should be avoided when the level is greater than 9 d/dL; however, the expert group acknowledged that evidence supporting the application of these permissive transfusion thresholds is weak and indeed the decision to transfuse in this setting is very rarely if ever based on hemoglobin level alone.

Anticoagulation. Lower flow venous pathways (Fontan) and the use of synthetic material in the circulation (prosthetic heart valves and goretex shunts) necessitate the use of anticoagulation to prevent thrombosis. Extracorporeal support devices (ventricular assist device [VAD] and extracorporeal membrane oxygenation [ECMO]) require anticoagulation in order to maintain device and cannula patency and integrity, as do IV catheters in certain higher risk patients, for example, where the central veins have been injured by multiple previous interventions. IV unfractionated heparin, an antithrombin 3 inhibitor, is the first-line anticoagulant, since it may be titrated and can easily be suspended with spontaneous effect reversal as required. The options for longer term anticoagulation include Coumadin, low-molecular-weight heparin, and antiplatelet agents including aspirin and clopidogrel.

Mechanical Circulatory Support. A significant evolution in the therapy available to pediatric critical care providers for the treatment of circulatory failure is MCS. The advancement in this modality parallels the advancement of critical care techniques. The first mention of MCS in *Critical Care Medicine* can be traced to 1977 (62), with the description of mechanical methods to influence pulmonary circulation by bed rotation and jet ventilation as an adjunct to cardiopulmonary resuscitation (CPR) (63). Although not necessarily thought of as “MCS,” these were the initial foray into the understanding that the circulatory system and cardiopulmonary interaction could be beneficially manipulated by external, mechanical modalities.

True progress of MCS occurred with the refinement of cardiopulmonary bypass. With work by Gibbon, Lillehei, and Kirklin, the realities of supporting DO_2 to the entire body for a temporary amount of time had been achieved (12, 64, 65). As these technologies were refined and became more portable, their applicability to the ICU setting became apparent. Bartlett was among the first to deploy ECMO in the care of patients (66). It is important to note that the earliest work done in this emerging field occurred in the pediatric domain (67, 68).

Although relatively portable, ECMO was still basically a cardiopulmonary bypass circuit applied outside the operating room and for a more prolonged period of time. True portability was achieved by the development of VADs in the 1960s (69, 70). This established the utilization of VADs for either bridge to transplantation or a destination as a replacement for a failing circulatory system. However, although “portable,” the first sets of devices were large, noisy, and full of complication risk; be it infectious or mechanical. Despite these initial limitations, work continued to improve the devices and led to a parallel broadening of indications for support (71, 72).

The history of development of VADs as a form of MCS in pediatric patients relates specifically to engineering advances leading to miniaturization of adult devices (73). The first wide clinical application of small VADs came with through the Berlin Heart Institute. With the publication of the results of the Berlin Heart trial, it was clear that children could be successfully supported with VADs, and following this success, other even smaller devices have begun to emerge (74, 75).

MCS devices now can be viewed as either temporary or durable. The time course associated with each is rather arbitrary and, for the purposes of critical care practice, have become less indicative of the device and more so the approach to deployment. Utilization of all forms of MCS, whether temporary or durable devices, is fundamentally different in the pediatric population and have driven the discussion around indications, effectiveness as a critical circulatory support tool, monitoring to guide timing of intervention, and long-term outcomes.

The original indication for MCS in the realm of critical care revolved around support from life-threatening circulatory collapse, specifically in the postoperative cardiac surgical patient (68). This success broadened the utilization of MCS to preoperative support for congenital heart lesions, myocarditis, septic shock, and ultimately extracorporeal CPR (15, 76). MCS has demonstrated relative success in measurable outcomes in each of these areas.

The successful expansion of indications for MCS in pediatric critical care has made an impact on the perception of cardiovascular support in pediatrics. The question of the superiority of inotropic or medical management versus mechanical intervention has led to further investigation of timing of deployment of

MCS. Through these investigations, the role and advancement of hemodynamic monitoring have been reframed to not only predict critical events but also guide intervention (77, 78). As is discussed elsewhere in this review, the field of pediatric critical care has evolved to utilizing monitoring modalities to not only predict the onset of complete failure or CPR but also now monitor to predict the optimum timing of deployment of MCS that will maintain an appropriate risk/benefit ratio.

The risks of MCS have segregated into two main categories: mechanical and hematologic. Mechanical complications include driveline issues, pump failures, and battery/electrical failures. These have been nearly completely eliminated as technology has advanced (79, 80). The more common and significant area of complications in MCS continues to be hematologic. The interaction among the pump, the blood, and the patient remains the Achilles heel of any device. The rate of significant clinical events related to bleeding, clotting, or embolic phenomena continues to be high (81).

Although management of these complications remains a challenge for the critical care practitioner, pediatric patients continue to benefit in both medium- and long-term outcomes. In evaluating 200 patients receiving primary durable devices, Blume et al (82) found an actuarial survival of 81% at 6 months. Competing risk analysis at 6 months revealed that 58% of patients had been transplanted, 28% were alive on support, 14% had died, and 0.6% recovered.

Future considerations of MCS in pediatric patients will continue to be driven by improved and miniaturized technology, improved safety profiles, and extension of the boundaries of both indication and duration for support (83).

Future Considerations and Challenges

Silbert et al (84) in 1969 state, “Our results reiterate the obvious suggestion that one must look beyond the preservation of physical life to ask at what price to future adaptation the child’s life has been spared.”

As we turn our attention to more granular components of outcome, we must focus not only on the short-term, hospital-based problems associated with complications of care but also on the long-term implications of pediatric cardiac critical care. For the cardiac intensivist, some consequences of surgery or intensive care may seem transient (e.g., reintubation

and infection), whereas others are more likely to result in longer lasting or even permanent impact (e.g., malnutrition and stroke). As more patients survive cardiac surgery specifically and cardiac intensive care in general, it has become clear that many of the seemingly “short-term” complications have longer term consequences. Improving “outcome” must, therefore, include reducing both the short-term frequency, as well as supporting ongoing investigation in the longer term consequences.

Phrenic nerve injury is known to cause respiratory failure and prolonged mechanical ventilation, particularly in neonates and infants. Diaphragm injury may occur following up to 5% complex repairs, particularly after reoperation frequently undergo diaphragm plication to aid in liberation from mechanical ventilation (85). Surprisingly, both medium- and long-term studies of the later impact of diaphragm paralysis are very limited. One study showed that, compared with patients with normal respiratory mechanics, patients with diaphragm paralysis had a more protracted course after the Fontan operation, due primarily to prolonged pleural drainage. Unfortunately, long-term studies of physical and psychosocial quality of life related to this relatively uncommon perioperative complication are lacking.

Venous thrombosis, either spontaneous or catheter-related, is a relatively common occurrence after cardiac surgery, occurring in up to 18% of children (86, 87). In addition to being related to infection and a longer duration of hospital stay, short-term problems include the frequent need for a second central line, and the use of anticoagulants and/or antiplatelet drugs over the short term. However, longer term problems include either difficult or prohibitive vascular access at future cardiac catheterizations or cardiac surgery, varicose veins, persistent ascites, nocturnal, or exercise-related leg pain (88). Catheter-related arterial thrombosis, particularly of the femoral artery, may occur in up to 4% of cases, especially in neonates and infants (89).

Acute kidney injury (AKI) is a relatively common complication following cardiac surgery in the neonate and young infant, occurring in 30–50% of cases. AKI is known to be associated with an increased risk of mortality, prolonged hospital stay, and costs, and the need for dialysis or renal replacement therapy and the overwhelming majority of patients are discharged with “normal” renal function based on serum creatinine

and other biomarkers (90, 91). There is growing evidence that chronic kidney disease (CKD) and hypertension are more common in survivors of CHD surgery with perioperative AKI, and the exact frequency of long-term CKD is only now being evaluated but also approaches 30–50% (92). The long-term effects of hypertension and CKD in the CHD population include an increased risk of AKI during follow-up surgery, increase in ventricular mass, decreased ventricular function, abnormal drug clearance, end-stage kidney disease, and a potential impact on cardiac transplantation status (93).

Although the above criteria of “successful outcome” are related directly to the surgical and ICU treatments of cardiac disease, the two most common and potentially disabling adverse long-term outcomes are as follows: 1) the long-term neurodevelopment of the patient and 2) the mental health and well-being of the family. These are particularly important “outcomes” to target, as some of the risk factors for adverse outcome are indeed modifiable, and the outcomes appear to be highly interrelated.

For the group of children with complex CHD, neurodevelopmental disabilities are common, affecting approximately half of the survivors as they mature. Formal evaluations of preschool and school-aged children, adolescents, and adults born with complex CHD all demonstrate an increased frequency of neurodevelopmental sequelae that may appear alone or in combination (**Table 1**). As children progress through school, low scores in terms of academic achievement, learning disabilities, behavioral problems, difficulties with social cognition, and attention deficit/hyperactivity disorder may result in academic failure, development of poor skills in both the classroom and socially, low self-esteem, behavioral disinhibition, and ultimate delinquency.

One of the greatest lessons learned through the development and evolution of cardiac critical care is that outcomes as defined by a binary measure of mortality are not the measure of success. Rather, we aim to achieve the outcome of a fully functioning member of society. We have learned to target quality outcomes.

The risk factors for adverse neurodevelopmental sequelae are multiple, cumulative, and, in some cases, ongoing. The challenge of course is to determine which of the known causes of increased risk are modifiable by those who work in cardiac intensive care. At the

TABLE 1.
Neurologic, Developmental, and Psychosocial Challenges Which Occur With Increased Frequency in Children, Adolescents, and Young Adults Born With Critical Congenital Heart Disease (Modified From Wernovsky and Licht [94])

Stroke
Seizures
Abnormal brain morphology and functional connectivity
Abnormal brain growth, cerebral atrophy
Oral-motor dysfunction
Poor head control
Delayed gross and fine motor milestones
Apraxia of speech
Clumsiness
Problems with visual-spatial-motor integration
Problems with executive function
Inattention and hyperactivity
Cognitive impairment, grade retention in school
Impaired memory
Autism spectrum disorders
Social awkwardness/impaired social cognition
CNS hemosiderin deposition
Premature dementia
Mental health problems, including mood and personality disorders
Decreased health-related quality of life

current time, there are multiple ongoing investigations regarding optimal timing of surgery, prevention of paradoxical emboli, maximizing CNS oxygen supply to demand, monitoring and preventing seizures, avoiding hyperventilation and alkalosis, investigation of the long-term effects of narcotics, sedatives, and other agents (versus the known sequelae of untreated pain on the brain), other environmental sources including plasticizers, noise, lack of circadian rhythm, lack of touch, and more (94). In essentially every study published on this topic, a unifying feature that increases

risk for neurodevelopmental disability is increased length of hospital stay.

Longer term effects of an ICU encounter include chronic stress and anxiety, financial concerns, disruption of daily living, post-traumatic stress syndrome, uncertainty, sleep problems, abnormal levels of maternal cortisol, and generalized maladjustment (95). Importantly, although the effects of cardiopulmonary bypass and surgery may explain up to 5% of the variance in long-term neurodevelopmental outcome, a study by McCusker et al (96) suggested that five statistically significant factors, together, accounted for nearly 60% of the variance seen on long-term behavioral outcomes: 1) parenting style (parental control), 2) marital status, 3) maternal worry, 4) cyanotic status, and 5) maternal mental health. It is clear that this stress begins at the time of diagnosis and is amplified during the period of critical illness.

Building on decades of experience in premature infants in the neonatal ICU, there has been an exponential growth of work being done to improve neurodevelopmental care in the cardiac ICU (CICU) and new recommendations to mitigate this stress are currently under implementation (97).

Hospital or 30-day survival is a necessary, but insufficient definition of outcome. The long-term neurodevelopment of the child, as well as the long-term psychosocial health of the family, must now be considered one of the most important elements in the delivery of quality care to our patients. Since the trajectory of life-long neurodevelopment, physical and mental health for critically ill children and their families starts in the CICU, long-term “well-being, of all organ systems (particularly the brain), and the family must be considered the most important outcome measure of cardiac intensive care in 2020 (98).

The discipline of *Pediatric Cardiac Critical Care Medicine* (PCCCM) has undergone considerably growth and maturation since the first dedicated CICUs were established in the early 1990s. Increasing disease complexity and severity of illness coupled with evolving comorbidities have provided the impetus for specializing care delivery for children with critical cardiac disease. The creation of pediatric CICUs, with specialized staff and resources as well as protocols and performance metrics specific to PCCCM, has increased dramatically since that time. In 2001, there were 21 freestanding units in the United States, and currently, there are upward of 55. There has been the emergence

of performance metrics specific to the care of children with critical cardiac disease, such as those created by the Pediatric Cardiac Critical Care Consortium, which has led to improved outcomes (44). In addition, specific treatment guidelines have been created, such as those by the American Heart Association for the resuscitation of children with cardiac disease (99).

Focused care delivery predictably has driven specialization in education and training (100). Textbooks and curricula have been published for physicians and advance practice providers. An international, multidisciplinary society was established in 2002, the Pediatric Cardiac Intensive Care Society (PCICS). The PCICS International Conference, which preceded the formation of the Society, debuted in 1996 with less than 100 attendees. The now annual conference (2020 will be the 16th) will exceed 700 attendees. Current expectations of the majority of heart centers in the United States are that new recruits receive training in so-called 4th-year programs in PCCCM following training in cardiology or critical care medicine categorical fellowship programs or complete training in both in lieu of a fourth year (100). The general consensus in the field is that an Accreditation Council for Graduate Medical Education-training platform will establish program standards and the creation of certification by way of an American Board of Pediatrics subboard will provide verification of initial training and continued competency (100). With further maturation of education and training, evolution of the field will be fully realized as expertise and collaborative networks grow, enhancing clinical research and quality metrics specific to PCCCM (101).

The evolution and advancement of the care of child with critical cardiac disease over the past 50 years has led to an amazing new patient population; the adult survivor of pediatric heart disease or the Adult with Congenital Heart Disease (ACHD). This development has demonstrated that we as pediatricians have succeeded in shepherding these patients to adulthood. Currently, over 90% of children with chronic pediatric diseases are now surviving into adulthood (102). For some conditions such as malignancy and cerebral palsy, admissions to pediatric institutions are growing at a faster rate in adult-aged patients than in children (103). This trend is also found specifically in the ACHD population (103, 104).

Ultimately, the ACHD patient lives in both the pediatric and adult healthcare worlds and this is especially apparent in times of critical illness. Evidence suggests

is that pediatric providers and hospitals provide the optimal care for ACHD patients (105, 106). Adult patients who are admitted to pediatric institutions have varying observed mortality (104, 107–109). These data are of particular importance to the critical care provider as it would appear that ACHD patients admitted to a pediatric institution have a higher than average severity and constellation of comorbidities (104).

The current state of ACHD patients admitted to PICU settings is only predicted to increase in magnitude (103, 110). This will lead to an opportunity to evolve critical care practice to meet the newly found demand. There are initiatives currently underway to define ACHD risk profiles, care models, outcome benchmarks, and unit subspecialization; all aimed at replicating the lessons learned by the evolution of cardiac critical care of infants and children over the past 50 years.

To conclude, we would argue that there are few areas of medicine and, specifically critical care that have demonstrated such incredible advancement over the past 50 years other than the care of children with critical cardiac disease. We have travelled a path that has gone from an expected mortality to an expected, though still elusive, perfect outcome in a matter of two generations.

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