Neurodevelopment in Congenital Heart Disease: Scope of the Problem

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Divisions of Cardiology and Critical Care Medicine
Ann & Robert H. Lurie Children’s Hospital of Chicago
### PCICS 14th Annual International Meeting

**Conflict of Interest Disclosures for Bradley S. Marino, MD, MPP, MSCE**

<table>
<thead>
<tr>
<th>Category</th>
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<td>Grant/Research Support</td>
<td>NIH x3 (U24, RO1, and R13)</td>
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<td>AHA SFRN Children’s Center</td>
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<td>Children’s Heart Foundation</td>
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<tr>
<td>Consultant</td>
<td>Novartis – LCZ696</td>
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<td>Speakers Bureau</td>
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<td>Stock Shareholder</td>
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<tr>
<td>Other (identify)</td>
<td>1. Philanthropic Support for NICU-Cardiac Neurodevelopmental Support Program</td>
</tr>
<tr>
<td></td>
<td>2. Creator of the Pediatric Cardiac Quality of Life Inventory</td>
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<tr>
<td></td>
<td>3. National leadership roles with the CNOC, AHA, AAP, and PCHA</td>
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</tbody>
</table>
Increasing Population of CHD Survivors
Quebec CHD Mortality in 1988 vs 2005

Dramatic Change in Survival over 15 yrs

1989 First Neonatal Surgical Case Series
Boston Children’s Hospital

Late Hazard

Early Hazard

Khairy et al, JACC 2010
STS Congenital Heart Surgery Operative Mortality

STS Period Jul 2013 - Jun 2017

Overall STS 3.2% Operative Mortality Rate Among High-Volume Centers

Ann & Robert H. Lurie Children’s Hospital of Chicago 1.5% Operative Mortality Rate

Low Volume Centers

High Volume Centers

Dotted line on graph represents overall value for the STS: 3.23%
Important Morbidities after Repair vs Palliation:

- Neurodevelopmental/Neurocognitive
- Psychosocial and Psychiatric
- Late surgery or catheter re-interventions
- Arrhythmias
- Chronic heart failure/transplantation
- Pulmonary hypertension
- Endocarditis
- Other important end organ dysfunction:
  - Chronic renal and liver insufficiency
  - Coagulopathy leading to thromboembolic complication
ND Phenotype in CHD Survivors

• Mild cognitive impairment - normal to slightly lower IQ and Academic Achievement
• Impaired pragmatic language
• Decreased visual construction and perception
• Poor executive functioning
• Inattention and increased impulsivity (ADHD)
• Diminished fine and gross motor skills
• Psychosocial maladjustment (internalizing problems)

Marino et al, Circulation, 2012
ND Phenotype in CHD Survivors

- Individual deficits or delays are may be mild, but often occur across multiple domains

- “High prevalence – low severity” picture doesn’t meet classic criteria of a “learning disability”

- Many of these children have difficulties in school, but may not qualify for special services
Psychosocial Phenotype in CHD Survivors

- Impaired social interaction and deficits in social cognition
  Bellinger et al, *Cardiology Young*, 2008

- Impaired core communication skills – incidence of autism spectrum disorders

- Increased incidence of Psychiatric disorders

- Issues with behavioral/emotional functioning
  - Anxiety
  - Depression
  - Post-traumatic stress
  Marino et al, *Circulation*, 2012
Prevalence of Neurodevelopmental Impairment in the CHD Population by Disease Complexity

Adapted from Wernovsky G. *Cardiol Young*. 2006;16 Suppl 1:92-104
The Rey Osterreith Complex Figure

- Tests visual construction and perception
  - visual-spatial
  - visual-motor
- Tests executive functioning
- Requires integration of many sections of the brain

Shin MS, Nat Protoc 2006
Rey-Osterrieth Figure: Visual Construction and Perception and Executive Functioning

Coutesy of Jane Newburger
Poor VCP and Executive Functioning

Rey-Osterrieth Copy Clinical Rating and Academic Success

% receiving remedial services

Clinical Rating of Rey

worst

best

clinical rating

I

II

III

IV

V

Visuospatial Memory Differs By Cardiac Diagnosis


**Structural Elements**

**Immediate Recall**

- SVF
- TOF
- TGA
- TD

Less Than Perfect (score ≤ 24) vs. Perfect (25)

*Courtesy of Jane Newburger, MD*
Executive Function

Inhibition

“Impulsive.”
“Has trouble waiting her turn.”

Working Memory

“Leaves his lunchbox, hat, jacket at school....every day!”
“Give him any more than 1 direction at a time and he’s completely lost.”

Cognitive Flexibility

“Gets upset by changes in plans.”
“Gets stuck even when the solution seems obvious.”

Cassidy et al, J Int Neuropsych Society 2015

• 80% of children with severe CHD are impaired in at least 1 measure of executive function
Attention Deficits – Increased Prevalence of ADHD

- CHD is associated with higher rates of ADHD - 30-50% in complex CHD, especially Fontan patients
- Most children with CHD can be safely treated with medication
- ADHD in CHD patients may not have the same underlying mechanisms as in the general population

(Mahle et al., 2000; Marino et al., 2012; Shillington, Glanzman, Ittenbach, Clancy, Gaynor, & Wernovsky, 2008)
Social Cognition

• “Theory of Mind” deficits – inability to read other people
  – Difficulties interpreting others internal states and actions
  – Difficulties identifying and describing their own internal state

• Difficulties processing and interpreting social situations and relationships

• Significant emotional and interpersonal difficulties

Belinger DC, Cardiol Young, 2008
“Reading the Mind in the Eyes Task”

bewildered
serious

ashamed
alarmed

Courtesy of Jane Newburger
## Associations Among CHD, ASD, ADHD, and Learning Disabilities in US Children Aged 2-17 Years, 1997-2011

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHD N = 374</th>
<th>No CHD N = 158,243</th>
<th>OR</th>
</tr>
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<tbody>
<tr>
<td>Autism/ASD</td>
<td>2.6%</td>
<td>0.6%</td>
<td>4.6 (1.9-11.0)</td>
</tr>
<tr>
<td>ADHD/ADD</td>
<td>10.3%</td>
<td>6.6%</td>
<td>1.6 (1.1-2.4)</td>
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<tr>
<td>Learning Disability</td>
<td>20.9%</td>
<td>7.6%</td>
<td>3.8 (2.9-5.2)</td>
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</tbody>
</table>
Causes of CNS Sequelae are Cumulative and Interactive

• Patient/Preoperative factors:
  − Genetic abnormalities, *in utero* factors, birth weight, gestational age, socioeconomic status, parental ability

• Global morbidity and sequelae of heart disease
  − Chronic severe cyanosis
  − Malnutrition
  − Arrhythmias
  − Cardiac arrest
Causes of CNS Sequelae Cumulative and Interactive (continued)

- Sequelae of cardiac interventions, such as cardiac surgery or catheterization
- Pre- and post-operative hemodynamic instability
  - Impaired cerebrovascular pressure autoregulation and reactivity to CO2
  - ↑ vulnerability to ↓ BP and ↓ CI

Cumulative White Matter Injury
Relationship Between Total Brain Volume and Gestational Age in CHD and Control Fetuses

Limperopoulos et al, *Circulation* 2010
Brain Maturation is Delayed in CHD

The brain of the term infant with complex CHD resembles that of a 35wk premature infant

Licht DJ et al, J Thorac Cardiovasc Surg 2009
An MRI Study of Neurological Injury Before and After Congenital Heart Surgery

William T. Mahle, MD; Federica Tavani, MD; Robert A. Zimmerman, MD; Susan C. Nicolson, MD; Kristin K. Galli, MD; J. William Gaynor, MD; Robert R. Clancy, MD; Lisa M. Montenegro, MD; Thomas L. Spray, MD; Rosetta M. Chiavacci, BSN; Gil Wernovsky, MD; C. Dean Kurth, MD

<table>
<thead>
<tr>
<th>TABLE 4. Incidence of Abnormalities on Brain MRI and MRS</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Lactate</td>
</tr>
<tr>
<td>Infarction</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>New</td>
</tr>
<tr>
<td>PVL</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>New</td>
</tr>
<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>New</td>
</tr>
<tr>
<td>Atrophy</td>
</tr>
</tbody>
</table>

Mahle WT, *Circulation* 2002
**Results:** Longer cardiac intensive care unit (CICU) LOS quartiles were associated at age 8 years with lower full-scale IQ (P = .02), lower verbal IQ (P = .02), and with tendencies toward lower performance IQ (P = .08) and math achievement (P = .08) in adjusted models.

**Conclusions:** Longer postoperative LOS is associated with worse later cognitive function, even when adjusted for perioperative events, perfusion times, and sociodemographic variables.
Widespread and Significant Reduction in Cortical and Subcortical Volume and Cortical Thickness in Fontan Survivors

Model for Neurobehavioral Dysfunction in CHD Surgical Survivors

- Hypoxemia
- Additional Surgery
- Socioeconomic Status
- Drug Exposures
- Developmental Interventions

Acquired White Matter Injury with Abnormal Microstructure and Decreased Connectivity

Susceptibility Genes

Home Environment Socioeconomic Status

Drug Exposures

Environmental exposures of CHD and its Treatment

Adapted from J. William Gaynor
Learning Challenges Are Common in CHD

- Students with complex CHD have generally lower academic achievement than typical peers
  - 1/3-1/2 of students with complex CHD receive special education programming
  - 1 in 6 are placed in substantially-separate classrooms
  - 1 in 5 repeat a grade at least once
  - 1 in 4 receive occupational therapy, physical therapy, speech therapy, and/or psychotherapy

Bellinger et al., 2011; Bellinger, Watson, et al., 2015; Jaworski, White, DeMaso, Newburger, Bellinger, & Cassidy, 2017; Shillingford et al., 2008
How Should We Measure Outcomes in Children with Heart Disease?

Health-related Quality of Life

- Pediatric Cardiac and CHD Population
  - Disease Complexity
    - Medical Surgical Catheter-based Therapy
      - Morbidity
        - Neurodevelopmental Morbidity
        - Psychosocial Morbidity
        - Physical Morbidity
      - Mortality
        - QOL
Definition of Quality of Life (QOL)

- Physical Health and Physical Functioning
- Psychological Functioning
- Social Functioning

QOL describes a child’s ability to function in situational contexts (family, school, peer) and derive personal satisfaction from doing so

Ware 1984, Aaronson 1988
Validation of the Pediatric Cardiac Quality of Life Inventory

Authors: Bradley S. Marino, MD, MPP, MSCE, a,b Ryan S. Tomlinson, BSE, a Gil Wernovsky, MD, c,a Dennis Drotar, PhD, a Jane W. Newburger, MD, MPH, f,g Lynn Mahony, MD, h Kathleen Mussatto, RN, PhD, i Elizabeth Tong, RN, MS, j Mitchell Cohen, MD, k Charlotte Andersen, RN, MS, a David Shera, ScD, l Philip R. Khoury, MS, a Jo Wray, PhD, m J. William Gaynor, MD, n Mark A. Helfaer, MD, o Anne E. Kazak, PhD, o and Judy A. Shea, PhD, p for the Pediatric Cardiac Quality of Life Inventory Testing Study Consortium

Divisions of a Cardiology, b Critical Care Medicine, and c Behavioral and Clinical Psychology, Department of Pediatrics, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio; Divisions of c Cardiology, Epidemiology and Biostatistics, and o Psychology, Department of Pediatrics, Division of Critical Care Medicine, Department of Anesthesiology and Critical Care, and

What’s known on this subject: Little is known regarding the impact of important clinical and patient factors (disease severity, medical care utilization, patient-parent consensus, and patient self-perception, competency, and behavior) on HRQOL in the pediatric cardiac population.

What this study adds: This large, multicenter study showed that lower HRQOL was associated with greater disease severity and medical care utilization, poorer patient self-perception and competency, and increased behavioral and emotional problems in the pediatric cardiac population. The PCQLI is valid and reliable.
Patient Independent ARC of QOL: Resilience vs Depressant Factors

Marino B, Moss and Adams’ 2013
Lower PCQLI Total Score Correlates with Worse Self-Perception and Behavioral and Emotional Functioning \([n=1,605]\)

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Domain</th>
<th>Respondent Group</th>
<th>Correlation Coefficient</th>
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<tr>
<td>SPPC/SPPA</td>
<td>Global Self Worth (\text{(Self-Perception)})</td>
<td>Child</td>
<td>0.49</td>
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<td></td>
<td></td>
<td>Adolescent</td>
<td>0.40</td>
</tr>
<tr>
<td>Achenbach</td>
<td>Total Competence Scale (\text{(Activity, Social, School)})</td>
<td>Child/Parent</td>
<td>0.31/0.33</td>
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<tr>
<td></td>
<td></td>
<td>Adolescent/Parent</td>
<td>0.31/0.38</td>
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<tr>
<td></td>
<td>Internalizing Problem (\text{(Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints)})</td>
<td>Child/Parent</td>
<td>-0.52/-0.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adolescent/Parent</td>
<td>-0.51/-0.51</td>
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</table>

*All comparisons significant <0.0001*

Marino et al, *Pediatrics* 2010
Lower PCQLI Total Scores Correlate with Increased Risk for Affective Disorder, Anxiety Disorder, and ADHD [n=1,605]

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Domain</th>
<th>Respondent Group</th>
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<tr>
<td>Achenbach (DSM)</td>
<td>Affective Disorder</td>
<td>Child/Parent</td>
<td>-0.55/-0.47</td>
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<td>Adolescent/Parent</td>
<td>-0.49/-0.51</td>
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<td>Anxiety Disorder</td>
<td>Child/Parent</td>
<td>-0.38/-0.44</td>
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<td>Adolescent/Parent</td>
<td>-0.37/-0.39</td>
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<tr>
<td></td>
<td>Somatic Problems</td>
<td>Child/Parent</td>
<td>-0.34/-0.34</td>
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<td>Adolescent/Parent</td>
<td>-0.36/-0.36</td>
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<tr>
<td></td>
<td>ADHD</td>
<td>Child/Parent</td>
<td>-0.33/-0.33</td>
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<td></td>
<td>Adolescent/Parent</td>
<td>-0.25/-0.24</td>
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</tbody>
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All comparisons significant <0.0001

Marino et al, *Pediatrics* 2010
Worse Executive Functioning is Associated with Worse PCQLI Total Scores and School Performance

The Journal of Pediatrics
Volume 173, June 2016, Pages 154-159

Original Article

Executive Functioning and School Performance among Pediatric Survivors of Complex Congenital Heart Disease

Portions of the study were presented at the scientific session and expo of the American College of Cardiology, April 2-5, 2011, New Orleans, LA.

Melissa Gerstle PhD 1, 2,*, Dean W. Beebe PhD 1, 2, Dennis Drotar PhD 1, 2, Amy Cassedy PhD 3, 4, Bradley S. Marino MD, MPP, MSCE 5, 6
Percentage of ND Patients “At Risk” for Problems with Motor, Mood, and Executive Functioning

Percent of ND Patients Scoring >1 SD Worse than the National Mean

- BOT Strength and Agility (scoring 40 or lower on the BOT test)
- CBCL combine MOOD (scoring 60 or above on the combined CBCL Mood questions)
- BRIEF MI (scoring 60 or above on the BRIEF MI test)

Motor | Anx/Depression | Executive Fxn
--- | --- | ---
2X | 2X | 3X

Population Base Rate
Multivariate Regression Models for PCQLI, PedsQL, and CBCL Patient and Parent-Proxy Scores

- **PCQLI Total Score**
  - Worse executive functioning (metacognition), gross motor ability, and mood were significantly associated and predicted an additional 47% of the variance ($\Delta R^2$) ($p < 0.01$)

- **PedsQL School Functioning and CBCL School Competence Scores**
  - Worse executive functioning (metacognition) was significantly associated for and predicted an additional 37-54% of the variance ($\Delta R^2$) ($p \leq 0.001$)

- Demographics and anatomy (age, gender, income, single ventricle) accounted for only 2-8% ($p < 0.05$) of the variance in QOL scores

Gerstle et al, J *Pediatrics*, 2016
QOL Conceptual Model in Pediatric Heart Disease

Pediatric Cardiac Population

Medical Surgical Catheter-based Therapy

Disease Complexity

Mortality

Morbidity

Psychosocial Morbidity

Neurodevelopmental Outcome
1. Intelligence
2. Academic Achievement
3. Neuropsychological Functioning
4. Gross Motor Functioning
5. Behavioral/Emotional Functioning

Characteristics of the Environment
1. Family Functioning
2. Parental Stress
3. Parental Post-Traumatic Stress
4. Parental Trait Anxiety and Depression
5. Parental Coping

Characteristics of the Individual
1. Self-Perception
2. Behavior
3. Post-traumatic Stress
4. Trait Anxiety

Interventions for ND and Psychosocial Phenotype Prevention

Interventions for ND and Psychosocial Phenotype Treatment

Physical Morbidity

HRQOL
“Nurturing” Neurodevelopmental and Psychosocial Resilience to Improve HRQOL

- Neurobehavioral and Psychotherapy in the child and adolescent to minimize impact of social cognition issues, psychiatric issues, autism spectrum and affective disorders, and ADHD

- Psychosocial support to have the child improve their self-perception

- Therapy in the patient and parent to:
  - Prevent and treat PTSD symptomatology prior to invasive procedures, in the ICU, and during follow-up
  - Prevent and treat Anxiety and depression

- Programs to reduce parental stress relative to raising a child with chronic disease
Adolescent ADHD and Adult Physical and Mental Health, Work Performance, and Financial Stress

Judith S. Brook, David W. Brook, Chenshu Zhang, Nathan Seltzer and Stephen J. Finch

Pediatrics 2013;131;5

- New York – Albany and Saratoga Counties
  - n=551: 72 ADHD+ / 479 ADHD controls
- Prospective cohort study: T1 14-16yrs and T2 37yrs
- ADHD+ had worse impaired physical and mental health
- ADHD+ had greater external stress with impaired work performance and higher financial stress
• Rochester Minnesota  
  − n=5,313: 367 ADHD+ / 4,946 ADHD controls
• Retrospective cohort study assessing Vital Status:  
  Age at FU 30yrs±1.9yrs
• ADHD+ had increased risk for mortality from suicide
• ADHD persisted into adulthood in 29.3% of the cohort
• ADHD+ had greater risk of psychiatric disorder – substance dependence, anxiety, and depression
Unifying Hypothesis of the Continuum of Neurodevelopmental to Neurocognitive Disease in the Lifespan of CHD Patients

Marelli et al, Circulation, 2016
Increased Risk of Dementia in ACHD Patients

Risk of Dementia in Adults With Congenital Heart Disease
Population-Based Cohort Study

BACKGROUND: More children with congenital heart disease (CHD) are surviving to adulthood, and CHD is associated with risk factors for dementia. We compared the risk of dementia in CHD adults to that of the general population.

METHODS: In this cohort study, we used medical registries and a medical record review covering all Danish hospitals to identify adults with CHD diagnosed between 1963 and 2012. These individuals with CHD were

Bagge CN, Circulation 2018
Increased Risk of Epilepsy Among Patients With Congenital Heart Disease

RESEARCH LETTER

Congenital Heart Defects and Risk of Epilepsy
A Population-Based Cohort Study

<table>
<thead>
<tr>
<th>Age of Study Subjects</th>
<th>Hazard Ratio (95% CI)*</th>
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<tr>
<td>0–4 y</td>
<td>3.7 (3.2–4.2)</td>
</tr>
<tr>
<td>5–32 y</td>
<td>2.3 (2.1–2.7)</td>
</tr>
<tr>
<td>Overall</td>
<td>2.5 (2.0–3.2)</td>
</tr>
<tr>
<td>Overall†</td>
<td>1.8 (1.5–2.2)</td>
</tr>
</tbody>
</table>

Although neurological morbidity has been consistently described in the congenital heart disease (CHD) population, no studies to date have examined the long-term risk of epilepsy in subjects with CHD compared with the general population. Previous studies, which point toward a heightened risk of epilepsy, include a single-center case series without the benefit of a control population and a subsequent population-based case-control study. Given the known clinical implications of epilepsy in the general population and the unique vulnerabilities of the CHD population, our study aimed to provide the first evaluation with the benefit of complete long-term follow-up to address the hypothesis that CHD is associated with an increased long-term risk of epilepsy.

Michelle Z. Leisner, MPH
Nicolas L. Madsen, MD, MPH
John R. Ostergaard, MD, DMSc
Jessica G. Woo, PhD
Bradley S. Marino, MD, MPP, MSCE
Morten S. Olsen, MD, PhD

Leisner MZ, Circulation 2016
AHA Scientific Statement

Neurodevelopmental Outcomes in Children With Congenital Heart Disease: Evaluation and Management

A Scientific Statement From the American Heart Association

This statement has been approved by the American Academy of Pediatrics.

Bradley S. Marino, MD, MPP, MSCE, FAHA, Co-Chair; Paul H. Lipkin, MD; Jane W. Newburger, MD, MPH, FAHA; Georgina Peacock, MD, MPH; Marsha Gerdes, PhD; J. William Gaynor, MD; Kathleen A. Mussatto, PhD, RN; Karen Uzark, PhD, CNP, FAHA; Caren S. Goldberg, MD, MS; Walter H. Johnson, Jr, MD; Jennifer Li, MD; Sabrina E. Smith, MD, PhD; David C. Bellinger, PhD; William T. Mahle, MD, FAHA, Co-Chair; on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council

Background—The goal of this statement was to review the available literature on surveillance, screening, evaluation, and management strategies and put forward a scientific statement that would comprehensively review the literature and create recommendations to optimize neurodevelopmental outcomes in the pediatric congenital heart disease (CHD) population.

Methods and Results—A writing group appointed by the American Heart Association and American Academy of Pediatrics reviewed the available literature addressing developmental disorder and disability and developmental delay in the CHD population, with specific attention given to surveillance, screening, evaluation, and management strategies. MEDLINE and Google Scholar database searches from 1966 to 2011 were performed for English-language articles cross-referencing CHD with pertinent search terms. The reference lists of identified articles were also searched. The American College of Cardiology/American Heart Association classification of recommendations and levels of evidence for practice guidelines were used. A management algorithm was devised that stratified children with CHD on the basis of established risk factors. For those deemed to be at high risk for developmental disorder or disabilities or for developmental delay, formal, periodic developmental and medical evaluations are recommended. A CHD algorithm for surveillance, screening, evaluation, reevaluation, and management of developmental disorder or disability has been constructed to serve as a supplement to the 2006 American Academy of Pediatrics statement on developmental surveillance and screening. The proposed algorithm is designed to be carried out within the context of the medical home. This scientific statement is meant for medical providers within the medical home who care for patients with CHD.

Conclusions—Children with CHD are at increased risk of developmental disorder or disabilities or developmental delay. Periodic developmental surveillance, screening, evaluation, and reevaluation throughout childhood may enhance identification of significant deficits, allowing for appropriate therapies and education to enhance later academic, behavioral, psychosocial, and adaptive functioning. (Circulation. 2012;126:1143-1172.)

Marino et al, Circulation, 2012
Congenital heart disease (CHD) algorithm for:
1. Surveillance
2. Screening
3. Evaluation
4. Management of developmental disorders and disabilities

Marino B S et al. Circulation 2012;126:1143-1172
Goals of ND Assessment in Pediatric Heart Disease and CHD Survivors

• To diagnose developmental disability and developmental delay through Surveillance, Screening, and Evaluation

• To put interventions in place to prevent or treat the ND and Psychosocial phenotype noted in the pediatric cardiac population to maximize long-term outcome
  – To maximize health-related QOL
  – To maximize educational attainment
  – To reduce the incidence of anxiety, depression, and stress in family members and family dysfunction
  – To maximize adult transition and ACHD outcome
Risk Stratification: High-Risk Patients

- Neonates or infants requiring open heart surgery (cyanotic and acyanotic types)
- Children with other cyanotic heart lesions not requiring open heart surgery in the neonatal or infant period
- Children with any combination of CHD and other co-morbidities
- Other conditions determined at the discretion of the medical home providers
Risk Stratification: High-Risk Patients

- CHD and ANY of the following co-morbidities
  - Prematurity (< 37 weeks)
  - Developmental delay recognized in infancy
  - Suspected genetic abnormality and/or syndrome
  - History of mechanical support (ECMO and/or VAD)
  - Heart transplantation
  - CPR at any point
  - Prolonged hospitalization (>2 week LOS in the hospital)
  - Perioperative seizures related to CHD surgery
  - Significant abnormalities on neuroimaging and/or microcephaly
ND Recommendations For Patients Stratified as High-Risk

• Referral to formal developmental and medical evaluation
• Referral to early intervention services or early childhood special education services prior to confirmation of a specific developmental diagnosis
• Periodic re-evaluations for DDs and developmental delays at 12-24 mo, 3-5 yrs, and 11-12 yrs of age
• Referral of young adults for higher education and/or vocational counseling
Monitoring and Intervening on Development

Cardiac ND Follow-Up Clinic at Ann & Robert H. Lurie Children’s Hospital of Chicago

- Offered to high risk NICU/Cardiac patients
- Regular developmental evaluations infancy through adolescence
- Psychology and Neuropsychology evaluation and management
- Physical, occupational, speech therapy
- Dieticians, social workers, nurses and APNs
- Care from Developmental Pediatricians and Special Educators

NICU-Cardiac Neurodevelopmental Program
Supporting development throughout childhood and adolescence
School Intervention Program Follow-Through

Educator In-Clinic

NICU-Cardiac Neurodevelopmental Program

Educator In-Community

Community Schools
Neurodevelopmental Evaluation without Communication to the Schools

HELLO? CAN ANYBODY HEAR ME?
Getting Patients into Clinics – The “Big Lie” and the “Grand Re-education”
Cardiovascular Care AND Neurodevelopmental and Psychosocial Support Across the Lifespan

Fetal Life  Neonate/Infant  Child/Adolescent  Adolescent-Young Adult

Fetal Clinic  Perioperative CICU  NICU-Cardiac Neurodevelopmental Program  Cardiovascular Bridge Programs

Comprehensive Cardiovascular Care AND Neurodevelopmental and Psychosocial Follow-up
Cardiac Neurodevelopmental Outcome Collaborative
Vision (Who we are)

“Multi-center, multi-national, multi-disciplinary group of healthcare professionals committed to working together and partnering with families to optimize neurodevelopmental outcomes for individuals with pediatric and congenital heart disease through clinical, quality, and research initiatives, intending to maximize QOL across the lifespan.”
Vision (Who we are)

“Multi-center, multi-national, multi-disciplinary group of healthcare professionals committed to working together and partnering with families to optimize neurodevelopmental outcomes for individuals with pediatric and congenital heart disease through clinical, quality, and research initiatives, intending to maximize QOL across the lifespan.”
CNOCK History

• 2012 AHA/AAP Scientific Statement entitled, “Neurodevelopmental Outcomes in Children With Congenital Heart Disease: Evaluation and Management”
  
  Marino et al, *Circulation* 2012

• 1st Cardiac Neurodevelopmental Symposium – Boston 2012 – 7th Annual CNOCK Scientific Sessions – Toronto October 2019

• CNOCK Incorporation 2015

• CNOCK Final Bylaw Approval, 501c3 status 2016

• First Elected Officers 2016; Second Elected Officers 2018 – Co-Chairs, Caren Goldberg, MD, MS and Erica Sood, PhD
3 Countries
33 Participating Institutions (↑20%)
630 Members (↑67%)
Infrastructure

- **Neurodevelopmental Core Lab — Children’s National Medical Center**
  - Neurodevelopmental and psychosocial data validation

- **Data Coordinating Center — University of Michigan**
  - Data validation and extraction in preparation for research and QI activities
  - Data integration with other members of Cardiac Networks United

- **Data Analytic Core — Boston Children’s Hospital**
  - Facilitation of grants
  - Analyses for clinical research
  - Analyses for quality Improvement science

- **Healthcare IT Solution — Arbormetrix**
  - Create data entry platform
  - Create data views/reports at patient, site, and collaborative level
  - Create CNOC and Site level dashboards
How will the CNOC Inform/Improve the lives of CHD Surgical Survivors?

• Next generation data of critical neurodevelopmental, psychosocial and QOL outcomes

• Longitudinal data across childhood and adolescence, ultimately into adulthood (across the lifespan) from >30 centers that will significantly increase our research and QI knowledge and capability

• Data that is important to parents and patients

• Natural choice to join the PC4/PAC3 dyad and Cardiac Networks United
CARDIAC NETWORKS UNITED

AN INTEGRATED PEDIATRIC & CONGENITAL CARDIOVASCULAR RESEARCH AND IMPROVEMENT NETWORK

Advisory Board Update
2/13/2018
The Future —
The NHLBI R13 Perspective

[Image of a road sign pointing to the future, present, and past]
Kansas City June 2018 – R13 Investigators
PIs Bradley S. Marino, MD, MPP, MSCE and Erica Sood, PhD
Six Working Groups

- **Fetal Brain Development and Neuroprotection**
  - Leads: Daniel Licht, MD & Catherine Limperopoulos, PhD

- **Surgical/Perioperative Neuroprotection and Neurodevelopment**
  - Leads: Bradley Marino, MD, MPP, MSCE, Richard Jonas, MD, & Dean Andropoulos, MD, MHCM

- **Characterization of Neurodevelopmental and Psychosocial Outcomes**
  - Leads: Jacqueline Sanz, PhD, ABPP-CN & Dawn Ilardi, PhD, ABPP-CN
Six Working Groups

- **Neurodevelopmental and Psychosocial Intervention**
  - Leads: Adam Cassidy, PhD, ABPP-CN & Jennifer Butcher, PhD

- **Family Stress and Coping**
  - Leads: Cheryl Brosig, PhD & Erica Sood, PhD

- **Neurodevelopmental Education, Outreach and Advocacy**
  - Leads: Janice Ware, PhD & Gretchen Carroll, MA
Critical Questions for the Next Decade

- Improve fetal brain development in children with CHD
- What is optimal timing for surgery requiring CPB for a neonate with complex CHD? Does timing vary by diagnosis, gestational age or other patient related factors?
- What is the best neuromonitoring strategies that can detect conditions of risk of hypoxic/ischemic neuronal injury and drive perioperative practices and personalized interventions to mitigate those risks?
- Will standardizing EEG utilization during the perioperative period improve ischemia and seizure identification and treatment, and protect the brain from injury and improve ND outcomes?
Critical Questions for the Next Decade

- How do deleterious genetic variants with high brain expression and/or inflammatory/resilience gene polymorphisms affect postoperative ND outcome?

- What interventions will improve ND and psychosocial outcomes that vary secondary to health disparities (e.g. language barriers, referral patterns, health literacy, and teenage/adult CHD)?

- What ND and psychosocial interventions will:
  - Minimize family stress and improve coping to improve the interaction of the parent-child dyad to maximize patient/parent psychosocial/psychiatric outcome and QOL
  - Mitigate neuropsychological issues especially executive functioning to improve ND outcome and QOL