Report from Evidence Review

Advisory Committee on Heritable Disorders in Newborns and Children

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Outline

- Case definition of critical congenital cyanotic heart disease
- Planned approach to the evidence review
- Preliminary findings regarding the accuracy of pulse oximetry
- Next steps

Overview

- Congenital heart disease (CHD)
  - spectrum of structural heart defects present at birth
- ***Critical*** congenital heart defects (CCHD) cause severe and life-threatening symptoms requiring intervention within the first year of life
- Critical congenital ***cyanotic*** heart defects
  - CCHDs that present with hypoxemia in most or all cases
- CHD affects
  - 7 to 9 of every 1000 live births in the US
  - about one-quarter have CCHD

Rationale for Review

1. CCCHD can cause significant morbidity and mortality
2. Newborn screening for CCCHD with pulse oximetry has been examined in several large studies
3. Early identification of infants with CCCHD may improve health outcomes

Case Definition

- Because of heterogeneity of CCCHD, we convened a Technical Expert Panel to refine case definition

Robert Beekman, III, MD, MS	Professor of Pediatric Cardiology, University of Cincinnati College of Medicine, Cincinnati, Ohio
Robert Koppel, MD	Attending Neonatologist, Regional Perinatal Center Director for Schneider Children's Hospital at Long Island Jewish Medical Center, New York
William Mahle, MD	Medical Director, Clinical Research, Pediatric Cardiologist, Sibley Heart Center Cardiology, Children's Healthcare of Atlanta, Atlanta, Georgia

CCCHD Case Definition

- A critical congenital heart defect requiring surgery or catheter intervention in the first year of life that presents with hypoxemia in most or all cases:
  - Outflow tract defects
    - Tetralogy of Fallot
    - D-transposition of the great arteries
    - Truncus arteriosus
    - Total Anomalous Pulmonary Venous Connection (TAPVC)
  - Right-sided obstructive defects
    - Tricuspid atresia
    - Pulmonary atresia, intact septum
  - Left-sided obstructive defects
    - Hypoplastic left heart

Preliminary Review: Materials Included

- Detailed literature review methods
- Summary of evidence from literature review
- Bibliography

Methods for Evidence Review

- Preliminary report (today)
  - Systematic literature review to summarize evidence from published studies on pulse oximetry screening
- Final report
  - Systematic literature review including natural history, diagnosis, treatment and economics of screening for CCCHD
  - Consultation with multiple CCCHD investigators and advocates and assessment of unpublished data

Methods for Literature Search

- Searched MEDLINE for all relevant screening studies published over a 20 year period
- Completed searches combining the National Library of Medicine Medical Subject Heading (MeSH) and keywords: "oximetry", "pulse", "pulse oximetry", "congenital", "heart", "disease", "congenital heart disease", "screening", and "newborn"
- Reviewed references from nomination form and bibliography of review papers
- Three investigators (AAK, ARK, DRM) reviewed all abstracts and independently abstracted a subset of the articles (20% overlap)

Systematic Literature Review Findings

- January 1990 – March 2010
  - Medline, OVID In-Process and Other Non-Indexed Citations
  - English language only
  - Human studies only
  - In cases of duplicate publications, selected the most recent or complete versions

- 73 abstracts selected for preliminary review
- 18 articles selected for in-depth review
- 11 articles met all inclusion criteria for abstraction

Papers Meeting Review Criteria

Study Design	Number of papers
Experimental intervention	0
Cohort study	0
Case-control study	0
Case series	0
Sample size ≤ 10	0
Sample size 11 to 50	0
Sample size 51 to 100	0
Sample size ≥ 101	0
Economic Evaluation	0
Cross-sectional study	11
Total studies	11

Quality Assessment Methods Used

- By Study Design
  - Compare within, not between, study design categories
- By Study Goal
  - Screening test
    - Example: Sensitivity and specificity of screening
      - Data obtained from screening program in U.S. population or similar
      - Data from systematic studies other than whole population screening
      - Estimated from known biochemistry of the condition

Quality Assessment: Screening Test

Type of evidence	Number of articles
Total	**11**
Overall sensitivity and specificity of screening	**11**
Data obtained from screening programs in U.S. population or similar.	2
Data from systematic studies other than from whole population screening.	9
Estimated from the known biochemistry of the condition.	0
False positive rate	**8**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than from whole population screening.	8
Estimated from the known biochemistry of the condition.	0
Repeat specimen rate	**1**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than whole population screening.	1
Estimated from the known biochemistry of the condition.	0
Second-tier testing	**5**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than whole population screening.	5
Estimated from the known biochemistry of the condition.	0
Other screening test characteristics	**0**

Adapted from Pandor et al. 2004, Pollitt et al. 1997

Screening Method

- First tier:
  - Pulse oximetry estimates the percentage of oxygen-saturated hemoglobin in the blood based on light absroption
    - Non-invasive
    - Usually takes minutes to measure
- Second tier:
  - Echocardiogram

  and/or
  - Clinical examination

Screening for CCCHD: Key Findings

Study's First Author	Location	Number Screened	Prevalence*	Age at Screening	Probe Location	Cutoff for normal	True Positive	False Negative	False Positive	True Negative	Fasle Positive Rate, %	Positive Predictive Value, %	Negative Predictive Value, %	Sensitivity, %	Specificity, %	Comments
Hoke 2002	Maryland, USA	2,876	7/10000	<6 hours, 24 hours and/or at discharge	H & F	≥92%	2	0	55	2,819	1.91	3.51	100.00	100.00	98.09	Counted FP as failed initial screen of POx with no CCCHD diagnosis
Richmond 2002	UK	5,622	12/10000	Between >2 hours and discharge; average 11.7 hours of age	F	≥95%	3	4	57	5,558	1.01	5.00	99.93	42.86	98.98	Counted FP as failed initial POx exam and failed second exam with no CCCHD diagnosis
Koppel 2003	New York, USA	11,281	4/10000	>24 hours of age or at discharge; average 72 hours of age	F	≥96%	3	1	1	11,276	0.01	75.00	99.99	75.00	99.99	
Reich 2003	Florida, USA	2,114	9/10000	>24 hours of age ; as close to discharge as possible	H & F	≥95%	1	1	3	2,109	0.14	25.00	99.95	50.00	99.86	
Bakr 2005	Saudi Arabia	5,211	8/10000	Prior to discharge; average 31.7 hours of age	H & F	≥94%	3	1	2	5,205	0.04	60.00	99.98	75.00	99.96	
Rosati 2005	Italy	5,292	2/10000	>24 hours of age or at discharge; median 72 hours of age	F	≥96%	1	0	2	5,289	0.04	33.33	100.00	100.00	99.96	Discrepancy between FP value stated in abstract and results
Arlettaz 2006	Switzerland	3,262	25/10000	6-12 hours of age; average 8 hours of age	F	≥95%	8	0	16	3,238	0.49	33.33	100.00	100.00	99.51	FP counted as ECHO done after failed POx exam with no CCCHD
Meberg** 2009	Norway	50,008	10/10000	6-16 hours of age	F	≥95%	44	6	NA	NA	NA	NA	NA	88.00	NA	Data for FP not given; unable to calculate
Sendelbach 2009	Texas, USA	15,233	1/10000	4 hours of age and pre discharge	F	≥96%	1	1	858	14,373	5.63	0.12	99.99	50.00	94.37	Counted FP as failed initial screen of POx with no CCCHD diagnosis
de Wahl Grannelli 2009	Sweden	38,429	3/10000	90% at <72 hours of age; median 38 hours of age	H & F	≥95%	10	0	77	38,270	0.20	11.49	100.00	100.00	99.80	72 inconclusive POx exams; not included in calculations
Riede 2010	Germany	41,445	3/10000	24-72 hours of age	F	≥96%	11	1	40	41,321	0.10	21.57	100.00	91.67	99.90	Counted FP as two failed POx exams with no CCCHD diagnosis

*Prevalence is calculated from screened asymptomatic new borns

**Unable to determine specific values for CCCHD only

H & F denotes right hand and foot; F, foot; FP; False Positive; POx, Pulse Oximetry; NA, Not available

Summary: CCCHD

- Wide range of calculated birth prevalence of CCCHD; ranging from 1 per 10,000 in a study conducted in Texas to 25 per 10,000 in a study conducted in Switzerland
- All but two studies report a specificity of >99%. The study with the lowest specificity (94%) screened within hours of birth, the other study reported a specificity of 98%.
- Sensitivity was more variable, ranging from approximately 42% to 100%. The reason for this variability is unclear.

Next Steps: Critical Evidence Needed

Remaining questions include:

- How much does pulse oximetry increase the number of cases identified in the newborn nursery
- Natural history, including spectrum of severity, of CCCHD not identified prenatally
- Does pre-symptomatic or early symptomatic intervention in newborns or infants with CCCHD improve health outcomes
- Economics surrounding newborn screening, diagnosis and treatment of CCCHD
- Identification of potential harms
- How available are diagnostic and treatment services

Next Steps: Experts and Advocates to Consult

Robert Beekman, III, MD, MS - University of Cincinnati College of Medicine, Cincinnati, Ohio

William Mahle, MD - Children's Healthcare of Atlanta, Atlanta, Georgia

Jane Newburger, MD, MPH - Children's Hospital Boston, Boston, Massachusetts

Jonathan Reich, MD, MS - The Watson Clinic LLP, The Watson Clinic Center for Research, Lakeland, Florida

Annamarie Saarinen, Parent advocate who is working to establish screening programs

Dorothy Sendelbach, MD - University of Texas Southwestern Medical Center, Dallas, Texas

- Other experts will be added to this list based on recommendations and as they are identified in the future literature searches

Thank You