Critical Congenital Cyanotic Heart Disease

Report from Evidence Review

Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

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Recent Progress and Activities

Critical Congenital Cyanotic Heart Disease

- Preliminary review presented in May 2010
- Final review presented today

Hemoglobin H Disease

- Manuscript submitted to *Journal of Pediatrics*

Neonatal Hyperbilirubinemia

- Evidence review in progress

Workgroup Team Members

Key authors:

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- Danielle Metterville, MS, MGH/Harvard
- Lisa Prosser, PhD, University of Michigan Health System

Program director:

- James M. Perrin, MD, MGH/Harvard

Staff:

- Marsha Browning, MD, MPH, MGH/Harvard
- Anne Marie Comeau, PhD, New England Newborn Screening Program/UMass Medical School
- Nancy Green, MD, Columbia University
- Denise Queally, JD, Consumer (PKU Family Coalition)

Materials Included in Final Review

- Detailed literature review methods
- Summary of evidence from literature review and expert unpublished data
- Tables highlighting key data from abstracted articles
- Bibliography

Overview

- Congenital heart disease (CHD)
  - Spectrum of structural heart defects present at birth
- ***Critical*** congenital heart disease (CCHD)
  - CHDs with severe and life-threatening symptoms requiring intervention within the first year of life
- *Critical* congenital ***cyanotic*** heart disease (CCCHD)
  - CCHDs that present with hypoxemia in most or all cases

- CHD affects
  - 7 to 9 of every 1000 live births in the US
  - Approximately 25% have CCHD

Methods of Evidence Review

- Systematic literature review
  - Summarizes evidence from published studies
  - Pulse oximetry screening literature review presented in May 2010
  - Natural history, diagnosis, treatment, economics and updated screening literature review presented today
- Consultation with multiple CCCHD experts to identify relevant unpublished data

Rationale for Review

1. CCCHD causes significant morbidity and mortality
2. Several large studies have examined newborn screening for CCCHD with pulse oximetry
3. Identification of CCCHD in neonates might improve health outcomes

Case Definition

- We convened a Technical Expert Panel to refine case definition and discuss pertinent key questions
- Case definition agreed upon by the ERG and the AC Nomination and Prioritization committee

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

CCHD 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:
  - Hypoplastic left heart syndrome (HLHS)
  - Pulmonary atresia, intact septum
  - Tetralogy of Fallot (TOF)
  - Total anomalous pulmonary venous return (TAPVR)
  - Transposition of the great arteries (TGA)
  - Tricuspid atresia
  - Truncus arteriosus

Other CCHD do not typically present with cyanosis and consequently are not reviewed

Systematic Literature Review Findings

- January 1990 – June 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

- 367 abstracts selected for preliminary review
- 67 articles selected for in-depth review
- 26 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	7
Sample size ≤ 10	
Sample size 11 to 50	
Sample size 51 to 100	
Sample size ≥ 101	7
Economic Evaluation	1
Cross-sectional study	11
Systematic Review	7
Total studies	26

Experts and Advocates

Robert Beekman, III, MD, MS

Elizabeth Bradshaw, MSN, RN, CPN

Robert Campbell, MD

Edward Clark, MD

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J. Philip Saul, MD

Dorothy Sendelbach, MD

Corrie Stassen

Barbara Stoll, MD

Arnold Strauss, MD

Lloyd Tani, MD

Ronald Woods, MD

Diane Zook, BS

Completed written survey/interview

Key Questions: Natural History

- What is the prevalence of CCHD among those neonates eligible for screening?
- What is the natural history, including the spectrum of severity, of CCHD among neonates eligible for screening?

Abstracted literature pertaining to Natural History

Type of evidence	Number of articles
Total	**11**
Review article	7
Multi-institutional case series (tricuspid atresia; pulmonary atresia; intact septum)	2
Single institution, largest case series available (TAPVR; truncus arteriosus)	2

*Also includes abstracted literature pertaining to Treatment

Natural History

Heart Defect	Hypoxemia	Ductal-dependent	Prevalence (per 10,000 live births)	Age at symptom onset	Untreated survival
HLHS	All	All	1 – 7	Immediately or within the first two months of life	Universally fatal if untreated
Pulmonary atresia, intact septum	All	All	0.7 - 0.9	Immediately	Neonate becomes severely ill when the ductus closes, leading to death
TOF	Most	Uncommon	3	Neonatal period	Amount of pulmonary blood flow obstruction determines onset and severity of symptoms
TAPVR	All	None	0.7 – 2.7	Immediately or within the first two months of life	Survival unlikely if untreated

Natural History

Heart Defect	Hypoxemia	Ductal-dependent	Prevalence (per 10,000 live births)	Age at symptom onset	Untreated survival
TGA	All	Uncommon	2 - 3	Immediately	Onset and severity of symptoms depend on anatomical and functional variants; if there is not adequate blood flow, the neonate will die
Tricuspid atresia	All	Some	0.7 - 2.7	Immediately or within the first two months of life	Cyanotic neonates that are ductal-dependent are critically ill
Truncus arteriosus	All	None	1.4 - 3.6	By two months of life	Fewer than 25% will survive past the first year of life without surgical intervention

Key Questions: Screening

- What is the accuracy of pulse oximetry in the newborn period for CCCHD? How does this vary by age of the neonate, placement of probes, and threshold value for action?
- How many additional cases of CCCHD would routine neonatal screening with pulse oximetry detect prior to hospital discharge, compared to current care, including screening prenatal ultrasounds and routine newborn clinical history and examination?
- What is the false positive and false negative rate of routine neonatal screening with pulse oximetry for CCCHD?
- What are the potential harms or risks associated with screening?

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 (pOx) estimates the percentage of oxygen-saturated hemoglobin in the blood
- Second tier (diagnostic)
  - Echocardiogram

Screening Literature: Numbers, Age, Cutoff, Prevalence

Study's First Author	Hoke 2002	Richmond 2002	Koppel 2003	Reich 2003	Bakr 2005	Rosati 2005	Arlettaz 2006	Meberg** 2009	Sendelbach 2008	de Wahl Grannelli 2009	Riede 2010
Number Screened	2,876	5,622	11,281	2,114	5,211	5,292	3,262	50,008	15,233	38,429	41,445
Age at Screening	<6 hours, 24 hours and/or at discharge	Between >2 hours and discharge; average 11.7 hours of age	>24 hours of age or at discharge; average 72 hours of age	>24 hours of age ; as close to discharge as possible	Prior to discharge; average 31.7 hours of age	>24 hours of age or at discharge; median 72 hours of age	6-12 hours of age; average 8 hours of age	6-16 hours of age	4 hours of age and pre discharge	90% at <72 hours of age; median 38 hours of age	24-72 hours of age
Cutoff for normal	≥92%	≥95%	≥96%	≥95%	≥94%	≥96%	≥95%	≥95%	≥96%	≥95%	≥96%
Location	Maryland, USA	UK	New York, USA	Florida, USA	Saudi Arabia	Italy	Switzerland	Norway	Texas, USA	Sweden	Germany
Prevalence*	7/10000	12/10000	4/10000	9/10000	8/10000	2/10000	25/10000	10/10000	1/10000	3/10000	3/10000
Probe Location	H & F	F	F	H & F	H & F	F	F	F	F	H & F	F

*Prevalence is calculated from screened asymptomatic newborns

**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

Screening Literature: True and False Positives and Negatives

Study's First Author	Hoke 2002	Richmond 2002	Koppel 2003	Reich 2003	Bakr 2005	Rosati 2005	Arlettaz 2006	Meberg** 2009	Sendelbach 2008	de Wahl Grannelli 2009	Riede 2010
True Positive	2	3	3	1	3	1	8	44	1	10	11
False Negative***	0	4	1	1	1	0	0	5	1	0	1
False Positive	55	57	1	3	2	2	16	NA	858	77	40
True Negative	2,819	5,558	11,276	2,109	5,205	5,289	3,238	NA	14,373	38,270	41,393
Comments	Counted FP as failed initial screen of POx with no CCCHD diagnosis	Counted FP as failed initial POx exam and failed second exam with no CCCHD diagnosis				Discrepancy between FP value stated in abstract and results	FP counted as ECHO done after failed POx exam with no CCCHD	Data for FP not given; unable to calculate	Counted FP as failed initial screen of POx with no CCCHD diagnosis	72 inconclusive POx exams; not included in calculations	Counted FP as two failed POx exams with no CCCHD diagnosis

**Unable to determine specific values for CCCHD only

***False negatives include: TOF (4), TAPVC (2), TGA (2), HLHS (1), Truncus arteriosus (1), Unknown (4)

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

Screening Literature: Test Characteristics

Study's First Author	Hoke 2002	Richmond 2002	Koppel 2003	Reich 2003	Bakr 2005	Rosati 2005	Arlettaz 2006	Meberg** 2009	Sendelbach 2008	de Wahl Grannelli 2009	Riede 2010
Fasle Positive Rate, %	1.91	1.01	0.01	0.14	0.04	0.04	0.49	NA	5.63	0.20	0.10
Positive Predictive Value, %	3.51	5.00	75.00	25.00	60.00	33.33	33.33	NA	0.12	11.49	21.57
Negative Predictive Value, %	100.00	99.93	99.99	99.95	99.98	100.00	100.00	NA	99.99	100.00	100.00
Sensitivity, %	100.00	42.86	75.00	50.00	75.00	100.00	100.00	89.80	50.00	100.00	91.67
Specificity, %	98.09	98.98	99.99	99.86	99.96	99.96	99.51	NA	94.37	99.80	99.90

**Unable to determine specific values for CCCHD only

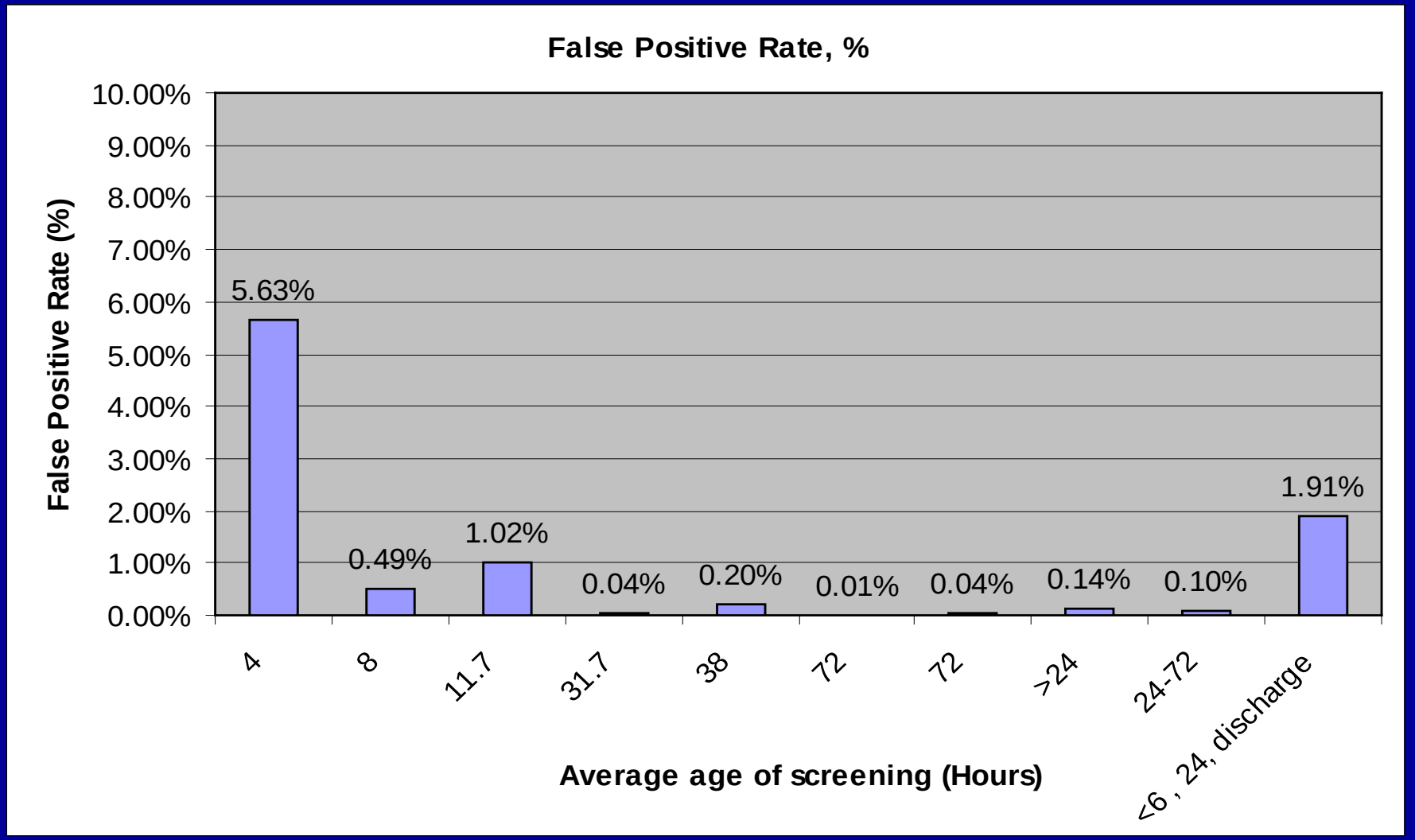
H & F denotes right hand and foot; F, foot;

FP; False Positive; POx, Pulse Oximetry; NA, Not available

Screening: Sensitivity

From 10 of the 11 identified screening literature studies; Meberg et al 2009 did not have all necessary data

Screening: False Positive Rate



From 10 of the 11 identified screening literature studies; Meberg et al 2009 did not have all necessary data

Screening: Clinical Exam vs. Pulse Oximetry

Data from Reich et al., 2003

Screened all newborns with pulse oximetry at a single institution during a one year period and compared the number of CHD diagnoses and echocardiograms to the previous year

Population	Assessments	Number of Echocardiograms (first 150 days of life)	Abnormal Echocardiogram	Significant CHD*
Study group (n = 2114)	Routine assessment + pulse oximetry	88	43/88 (48.8%)	12/88 (13.6%)
Comparison group (n = 2851)	Routine assessment alone	108	42/108 (38.9%)	13/108 (12%)

*Significant CHD defined as those requiring medical or surgical management

Overall, no statistically significant differences between the study and comparison group

Screening: Clinical Exam vs. Pulse Oximetry

Data from Bakr & Habib, 2005

Assessed the utility of pediatrician-provided clinical exam alone, pulse oximetry alone, and combined clinical exam and pulse oximetry screening for the detection of CHD in 5211 newborns

	Pulse oximetry	Clinical exam	Combined
Sensitivity	30.8%	46%	77%
Specificity	99.9%	99.8%	99.7%
Positive Predictive Value	80%	60%	66.7%

Pulse oximetry detected cases of pulmonary atresia, TAPVR and truncus arteriosus that clinical exam did not detect.

Acyanotic CHD, such as septal defects, were detected by clinical exam only.

Screening: Unpublished Data

- Experts reported that in the regions of their practices, more than half of CCCHD cases are diagnosed prenatally
- Prenatal ultrasounds look at the four chamber view of the heart, and may miss conditions such as:
  - TAPVR
  - TGA
  - Truncus arteriosus
- No follow up data available from pilot pulse oximetry screening programs

Key Questions: Diagnosis

- How available is echocardiography to evaluate those with a positive pulse oximetry screening result?

Diagnosis Literature

- Echocardiography is the diagnostic test for CCCHD
- Allows for confirmation of the CCCHD in addition to structural and functional characterization
- Did not identify evidence regarding the availability of echocardiography and pediatric cardiology services in birthing hospitals in the United States

Diagnosis: Unpublished Data

- Discussion of emerging use of internet-based picture archiving and communications systems (PACS) for distant interpretation of echocardiograms

- Little available information regarding smaller vs. larger birthing hospitals and access to echos

Key Questions: Treatment

- Does pre-symptomatic or early symptomatic intervention in newborns or infants with CCCHD improve health outcomes?

- What is the availability of treatment?

Abstracted literature pertaining to Treatment

Type of evidence	Number of articles
Total	**11**
Review article	7
Multi-institutional case series (tricuspid atresia; pulmonary atresia; intact septum)	2
Single institution, largest case series available (TAPVR; truncus arteriosus)	2

*Also includes abstracted literature pertaining to Natural History

Treatment Literature

Heart Defect	DA Dependent	Treatment	Typical age at intervention	Reported Mortality
HLHS	All	3-step surgical staged intervention or primary cardiac transplantation	During infancy	**Surgical:** Currently around 65% at 5 years of age and 55% at 10 years of age **Transplant**: mortality while awaiting transplant is 21% to 37%
Pulmonary atresia, intact septum	All	Sequence of surgical procedures dependent on the morphology	98% of reported cases within the first 7 days of life	81% at one month, 72% at six months, 69% at one year, 66% at two years and 64% at two years
TOF	Uncommon	Complete surgical repair	4-6 months	25-year survival rates are as high as 94%
TAPVR	None	Complete surgical repair	During infancy	Survival was 68% at 1 year, and 65% at 14 years after surgery Postoperative 5-year survival for since 2000 is 97%

Treatment Literature

Heart Defect	DA Dependent	Treatment	Typical age at intervention	Mortality
TGA	Uncommon	Balloon atrial septostomy followed by surgical correction	Soon after birth and correction later in infancy	Long-term event-free survival is approximately 88% at both 10 and 15 years of age
Tricuspid atresia	Some	Sequence of surgical procedures dependent on the morphology	During infancy	Overall survival at 5 years was 86%
Truncus arteriosus	None	Complete surgical repair	During infancy and primarily in the neonatal period	Actuarial survival among infants was 90% at 5 years, 87% at 10 years and 83% at 15 years

Treatment: Unpublished Data

- Experts corroborated that each of the heart defects have surgical interventions that improve outcomes

- They did not identify any direct data regarding whether detection of CCCHD by pulse oximetry leads to improved health outcomes compared to those that are detected clinically

Key Questions: Economics

- What are the costs associated with the screening test?
- What are the costs associated with failure to diagnose in the pre-symptomatic period?
- What are the costs associated with treatment?
- What is the cost-effectiveness of newborn screening for CCCHD?

Quality Assessment: Economics

Type of evidence	Number of articles
Total	**1**
I. Evaluation of important alternative interventions comparing all clinically relevant outcomes against appropriate cost measurement and including a clinically sensible sensitivity analysis.	1
II. Evaluation of important alternative interventions comparing a limited number of outcomes against appropriate cost measurement, but including a clinically sensible sensitivity analysis.	0
III. Evaluation of important alternative interventions comparing all clinically relevant outcomes against inappropriate cost measurement, but including a clinically sensible sensitivity analysis.	0
IV. Evaluation without a clinically sensible sensitivity analysis	0
V. Expert opinion with no explicit critical appraisal, based on economic theory	0

Adapted from NHS Centre for Reviews and Dissemination Report 4, March 2001

Economics

- One cost-effectiveness study identified: Griebsch et al., Int J Tech Assess Health Care, 2007

- Study Design:
  - UK setting
  - Health system perspective
  - Decision analysis

- Screening strategies evaluated:
  1. Clinical examination alone
  2. Clinical examination with pulse oximetry (within 24 h)
  3. Clinical examination with screening echocardiography (within 24 h)

Economics cont.

- Projected number of timely diagnoses per 100,000 newborns screened:

Clinical examination alone:	34.0
Clinical examination w/pulse oximetry:	70.6
Clinical examination w/screening echo:	71.3

- Cost per timely diagnosis:

Clinical examination w/pulse oximetry:	£4894
Clinical examination w/screening echo:	£4,496,666

- Conclusions for UK setting:
  - Screening with pulse oximetry in addition to clinical examination was cost-effective
  - Screening with echocardiography was not cost-effective under current conditions for test cost and performance

Condition Key Findings

- For the seven CCCHD reviewed
  - Onset of symptoms all occur within the neonatal period
  - Symptom onset ranges from birth to appearing healthy until a few months of age when the infant presents with symptoms
  - Onset and severity may depend upon the anatomical and functional variants

Screening Key Findings

- For the eleven screening studies reviewed
  - All but two pulse oximetry studies reported a specificity of greater than 99%
  - Sensitivity ranged from 42% to 100% with no clear explanation for the variability
  - CCCHD most often reported as undiagnosed by physical exam alone were TGA and TAPVR
  - Pulse oximetry appears to identify neonates with CCCHD that prenatal and clinical exam alone may miss

Treatment Key Findings

- All of the lesions identified in the case definition have surgical interventions
- Timing of surgical intervention all occurs within infancy and most soon after birth.
- Rates of success and mortality vary among the procedures and include variable long-term morbidities

Economics Key Findings

- The conclusion of the one economic study identified was that screening with pulse oximetry in addition to clinical examination was cost-effective compared to usual care

Questions

- How does screening test accuracy vary by the age of the neonate, in conjunction with placement of the probes, and threshold value for action?
- How does prenatal screening and detection of CCCHD affect the sensitivity, specificity, positive predictive value, and negative predictive value of postnatal pulse oximetry screening of asymptomatic newborns?
- What are the differences in benefits and disadvantages of prenatal diagnosis versus early postnatal diagnosis of CCCHD?

Questions

- How available is echocardiography to evaluate those with a positive pulse oximetry screening result?
- Is telemedicine a practical alternative for birth hospitals without access to pediatric cardiology services?
- What is the availability of treatment?
- What are the costs associated with treatment?
- What are the costs associated with failure to diagnose in the pre-symptomatic period?

Key Questions

- What is the evidence that using pulse oximetry adds to the clinical exam?
- What methods exist to improve false positive rates?
- What is the availability of follow-up and diagnosis?
- What is the evidence that early intervention is beneficial?

Thank you

Strength of Evidence for Key CCCHD Questions

Number of studies; subjects	Design	Risk of bias/study quality	Consistency	Directness	Precision	Strength of evidence
Additional sensitivity of pulse oximetry over clinical exam						Moderate
3; 45,754	Prospective Cohort	Good	Inconsistent	Direct	Imprecise	-
Evidence Summary: Pulse oximetry detects most cases of CCCHD. Most studies suggest that pulse oximetry leads to the detection of additional cases over those detected by clinical examination.						
Specificity of pulse oximetry						Moderate
11; 180,773	Prospective Cohort	Good	Inconsistent	Direct	Imprecise	-
Evidence Summary: The specificity of pulse oximetry after 24 hours is high.						
Availability of follow-up care						Poor
0;0	N/A	N/A	N/A	N/A	N/A	-
Evidence Summary: No data identified regarding the availability of follow-up diagnostic care for those with a positive screen.						
Effectiveness of early intervention						Fair
N/A	Case series and reviews	N/A	N/A	N/A	N/A	-
Evidence Summary: Indirect evidence that early intervention is associated with improved outcomes for those with CCCHD.						