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Neoreviews 2012;13:e724
DOI: 10.1542/neo.13-12-e724

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Oxygen Saturation Screening for Critical Congenital Heart Disease

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Educational Gaps

1. Prenatal diagnosis of CCHD in the United States is 25% to 50%. Clinical examination remains nonspecific and insensitive. Does universal saturation screening provide additional opportunity to prevent neonatal mortality from undiagnosed CCHD?
2. There is no linkage of the oxygen saturation screening and birth hospital data to congenital heart disease databases and registries to identify all false-negative cases.
3. Cost-effectiveness data for oxygen saturation screening are lacking, particularly regarding the cost of long-term mortality and morbidity related to delayed diagnosis.

Abstract
Critical congenital heart disease (CCHD) refers to lesions of the cardiovascular system, present at birth, which if left untreated in early infancy, will severely compromise the infant’s well-being and survival. Transposed great arteries, hypoplastic left heart, total anomalous pulmonary venous drainage, coarctation of the aorta, and interrupted aortic arch account for more than 70% of CCHD. Until recently, clinical examination followed by blood gas analysis (100% oxygen challenge) and echocardiogram have been the mainstays for diagnosis. However, these methods are unsatisfactory in preventing missed diagnosis before discharge in hospital-born infants. Prenatal diagnosis results in 25% to 50% detection of CCHD in the United States at the present time. In the last 10 to 15 years, noninvasive transcutaneous pulse oximetry has provided the means and impetus for blood oxygen saturation screening as an adjunct to traditional screening methods. It now seems that sufficient evidence exists to embrace universal oxygen saturation screening as one of the newborn screening tests before discharge from the hospital. The optimal method for universal oxygen saturation screening remains debatable, continues to be studied, and is evolving. Nevertheless, the current state of universal oxygen saturation screening should help provide reassurance to the scientific, medical, and health policy communities that this is yet another example of good preventive medicine at work in pediatrics and newborn medicine.

Objectives
After completing this article, readers should be able to:
1. Define critical congenital heart disease (CCHD) and recognize its clinical importance.
2. Describe current knowledge gaps in optimal universal screening for CCHD.
3. Understand limitations of universal oxygen saturation screening in detecting CCHD.
4. Describe performance test characteristics for universal oxygen saturation screening based on the most recent evidence-based reviews.

Introduction
Consensus statements by the American Academy of Pediatrics and the American Heart Association support a growing movement regarding universal oxygen saturation screening...
for critical congenital heart disease (CCHD) currently detected by using transcutaneous pulse oximetry. (1)(2)(3) There is good evidence (2)(3) for universal screening, but cost-effectiveness data remain a concern. In the United Kingdom, previous estimates (4) suggested lack of cost-effectiveness, but more recent estimates indicate otherwise. (5)(6) Data from Sweden (7) imply that the screening programs are cost-effective, and several European nations have embraced universal screening. (8)(9) Preliminary data from the United States suggest that such screening is likely to be cost-effective. (10) The United States, along with other nations with much larger populations of live births (e.g., China), are now beginning to initiate universal oxygen saturation screening programs in newborns.

Definition
Congenital heart disease (CHD) affects 8 per 1,000 live births and refers to structural disorders of the heart and great vessels that are present at birth. Globally, CHD affects over one million live births annually and is the leading cause of infant mortality attributable to birth defects. (11) Although there is no universally agreed upon definition of critical CHD (CCHD), it usually refers to CHD that requires surgical or interventional cardiologic management in the first year after birth, typically in early infancy, to prevent mortality and/or severe morbidity. The most common types of CCHD include transposition of the great arteries (TGA), hypoplastic left heart (HLH), total anomalous pulmonary venous drainage, and coarctation/interruption of the aorta. Pulmonary atresia, tricuspid atresia, critical obstruction of either ventricular outflow tracts, and several other complex cardiac lesions are less common forms of CCHD.

Advocacy for Universal Oxygen Saturation Screening
Universal newborn screening has its roots in parent advocacy, and universal oxygen saturation screening is no exception. Mothers and families with infants affected by CCHD, some of whom did not survive infancy, were led by Annamarie Saarinen and inspired the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children to add CCHD to its list of disorders that receive universal screening before hospital discharge. By early 2010, persuasive arguments had been made by pediatric cardiologists in the lay press (12) and in the medical literature: “There is no reason not to use pulse oximetry in the newborn nursery.” (13) The delay of universal screening for CCHD in the United States has been compared with delays in instituting the “Back to Sleep” campaign for sudden infant death syndrome, and the implications for mortality may be parallel. Affected mothers also enlisted the help of US institutions already involved in universal screening, including those led by a pediatric cardiologist in Washington, DC, as well as our own early experience from San Jose, California. In October 2010, these combined advocacy efforts led to the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children recommendations to Health and Human Services Secretary Kathleen Sebelius to include CCHD in universal screening. Subsequently, several stakeholders from affected families, governmental agencies, the March of Dimes, professional societies, industry, and others have had two meetings at Heart House, the headquarters for the American College of Cardiology in Washington, DC (under the leadership of the American Heart Association, the American College of Cardiology, and the American Academy of Pediatrics) in January 2011 and February 2012 (Fig 1). Currently, efforts are underway to shape national legislation in health policy in several states, actively led by parent advocacy groups such as the Newborn Coalition and 1:100, which maintain updates of progress on the national front (Fig 2).
Epidemiology and Global Perspective

Prenatal Detection
Up to 25% to 30% of CHD detected in the first month after birth may be critical. Current national estimates of prenatal detection of CCHD are as low as 25%, with best published US estimates at 50%. (14) There exists much promise for improved antenatal detection rates (15) with outflow tract views (91% sensitivity) compared with four chambered views (63% sensitivity). Other studies, however, have found that the average time for transfer of this kind of evidence to widespread practice is 17 years. (16)

Mortality and Morbidity
Historically, TGA and HLH are the leading causes of death due to CCHD. It is known that the most severe of cardiac lesions (17) may be masked by an initially well-appearing infant with sudden onset of decompensation a few hours to days after birth. Data from 898 infants in California (18) who died of CCHD at age 1 to 364 days included 152 infants with a missed CCHD diagnosis at a median age of 13.5 days; data were from 1984 to 2004. More than one half of these infants died at home or in a hospital emergency department. Although the annual number of these deaths declined in 1989 to 1999, the number remained unchanged from 2000 to 2004. Most deaths were attributable to HLH and coarctation of the aorta. Up to 30 deaths per year in California were attributable to missed or late diagnoses of CCHD, leading to an overall incidence of missed CCHD of 1.7 per 100,000 live births. Extrapolated to national live birth rates, the absence of universal oxygen saturation screening could lead to at least 70 to 100 infant deaths due to undiagnosed CCHD, leading to an overall incidence of missed CCHD of 1.7 per 100,000 live births. Extrapolated to national live birth rates, the absence of universal oxygen saturation screening could lead to at least 70 to 100 infant deaths due to undiagnosed CCHD. (19) between 2002 and 2006. Obstruction to the left side of the heart was again the most common cause.

In contrast to the US experience, a large Swedish study (7) found that there were no deaths (of 60 overall) from undiagnosed duct-dependent circulation in West Gotaland, where universal oxygen saturation screening was performed (N = 39,821) compared with 5 deaths (of 100 overall) from other Swedish regions that did not screen. Thus, estimate of deaths due to unrecognized duct-dependent circulation from these other referring regions was 4.6 per 100,000 live births (95% confidence interval [CI]: 0.6–8.6). This study offers hope that universal oxygen saturation screening might have the potential to reduce or near-eliminate deaths due to undiagnosed CCHD.

Figure 2. Critical congenital heart disease (CCHD) screening legislation in different states. Reprinted from cchdscreeningmap.com.
It seems logical to propose that early detection would help to minimize morbidity and alleviate some of the stress in parental experiences. Delayed diagnosis worsens the preoperative condition and postoperative outcome of newborns. Prenatal diagnosis of TGA has been associated with decreased mortality and morbidity due to earlier diagnosis, treatment, and prevention of preoperative complications. An unanswered question about universal oxygen saturation screening is whether there is more benefit compared to risk of iatrogenic harm accompanied by early diagnosis. This question is true for prenatally detected CHD as well. Although population-based studies have shown no benefit from the level of care at the birthing hospital in those prenatally diagnosed with CHD, there are practical considerations such as postnatal transport. A single-center retrospective review of 202 infants receiving prostaglandin E₁ suggests that “the risks of prophylactic intubation before the transport of otherwise stable infants on prostaglandin E₁ must be weighed carefully against possible benefits.”

**Oxygen Saturation Screening Method: Evidence-Based Review**

**Screening Test Characteristics**

Sensitivity of oxygen saturation screening was most recently estimated at 76.5% (95% CI: 67–83.5), with a specificity of 99.9% (95% CI: 99.7–99.9). The false-positive rate in this recent meta-analysis was estimated at 0.14% (95% CI: 0.06–0.33). The false-positive rate at 24 hours, as estimated by using mathematical modeling and in study conditions with screening at 24 hours, was as low or lower than 0.01% (or 1:10,000). In the United States, accurate data on the false-negative rate will require linking newborn oxygen saturation screening data to existing agencies devoted to improving CHD care, such as the Society of Thoracic Surgeons’ national database and the Improving Pediatric and Adult Congenital Treatment registry.

A recent meta-analysis of 13 eligible studies included 229,491 infants who underwent universal oxygen saturation screening. These studies included 151 infants detected with CCHD (a prevalence of 1:1,500). When the three studies that involved prenatally diagnosed lesions were excluded, the prevalence of CCHD lesions detected with universal oxygen saturation screening was 114 of 190,867 infants screened (1:1,700). Of these 114 infants, 88 were true-positives (77.2%) and 26 were false-negatives (22.8%). Thus, universal oxygen saturation screening will pick up the majority of CCHD while missing up to 1 in 4 to 5 infants who have the disease. The supplementary appendix as provided by the authors is illuminating for the types of lesions detected (true-positives) or missed (false-negatives). The majority of false-negatives included coarctation of the aorta or interrupted aortic arch. Thus, coarctation and aortic arch interruption remains the Achilles’ heel of universal oxygen saturation screening for CCHD. Figure 3 illustrates the frequency distribution of CCHD, although it oversimplifies the complexity of the CCHD lesions detected.

**Methods of Screening**

Different strategies using preductal and postductal versus postnatal alone have used varying saturation thresholds to detect CCHD. Postnatal screening alone has been recommended by some authors but not by others. Some of the fundamental findings regarding distribution of oxygen saturation come from studies that measured oxygen saturation in the first 24 hours after birth. Preductal oxygen saturation is higher than postductal in the first 4 hours after birth. This difference has been shown to disappear by 24 hours of age. Our experience from screening more than 12,000 newborns is that postductal oxygen saturation is greater than or equal to preductal saturation in 78% of newborns screened between 18 and 60 hours after birth. Figure 4 summarizes data from three studies that measured preductal and postductal oxygen saturation in the first 24 to 60 hours after birth. It illustrates that the direction of the difference between preductal and postductal saturation varies with postnatal age. The clinical significance, physiological explanation, and validity of these findings bear further exploration. Better understanding of such physiological variability is essential for defining threshold criteria for universal oxygen saturation screening. With widespread adoption of universal screening, it is critical to collect and evaluate oxygen saturation values in large populations to determine optimal screening methods.

Current evidence suggests that despite the universal oxygen saturation screening used, serial physical examinations remain crucial to narrowing the diagnostic gap and maximizing sensitivity in detecting CCHD. A comprehensive clinical evaluation that includes environmental exposures, family history, and other anomalies is essential. While most CHDs are non-syndromic, isolated lesions, both syndromic and isolated lesions may have an underlying molecular genetic defect. Thus, early involvement of a dymorphologist/geneticist is essential to optimal management. The molecular genetics for CHD are rapidly expanding and have been extensively reviewed.
Screening Equipment and Technology

Current universal oxygen saturation screening uses pulse oximetry to measure oxygen saturation. Knowledge of the type of oxygen saturation measured in the institutional screening device is essential. When defining threshold values for pulse oximetry screening for CCHD, consideration needs to be given to the type of oxygen saturation that is displayed: functional versus fractional. (25) Functional saturation measures the oxyhemoglobin and reduced hemoglobin alone, and fractional saturation measures the oxyhemoglobin and reduced hemoglobin, and approximates carboxyhemoglobin and methemoglobin. Hence, functional oxygen saturation tends to be 1.6 to 2 points higher than the fractional oxygen saturation. (36) Motion artifact and different averaging time of the pulse oximeter may also influence saturation readings. Longer (8–10 seconds) time averaging is preferable in this context (7), whereas shorter (2 seconds) time averaging has traditionally been used in the delivery room to obtain the quickest possible reading. There may be another 2% discrepancy between pulse oximetry saturation and arterial saturation by co-oximetry, with an increasing bias at lower oxygen saturation levels. (37) Understanding these technical differences in the devices used is critical to standardizing screening methods to detect CCHD.

Peripheral perfusion index (PPI) is an indirect, non-invasive measure of peripheral perfusion, expressing pulsatile signal as a percentage of nonpulsatile signal. (38) PPI is one potential opportunity for exploration in CCHD screening. Many institutions, including those presently screening for CCHD, have monitors capable of this function. De-Wahl Granelli established a nomogram from 10,000 healthy newborns and found that five of nine left heart obstructive lesions had abnormal PPIs less than 0.7. (39) Our nomogram in over 90 healthy newborns in the
first 45 minutes after birth (40) found that preductal PPIs are similar to those described by de-Wahl Granelli in infants between 1 and 120 hours after birth. Our preliminary observation in two infants, one with coarctation of the aorta and the other with interrupted aortic arch, showed pre- and postdifferential PPIs independent of oxygen saturations that led to the clinical diagnosis of aortic arch obstruction before echocardiography.

Future Directions

Universal oxygen saturation screening for CCHD in newborns is gaining acceptance in much of the industrialized world. The optimal timing, protocols, and methods continue to evolve. In the context of newborn screening in general, this remains the second point-of-care test after the newborn hearing screen, and thus it presents its own unique challenges, different from traditional blood spot screens. HLH and coarctation of the aorta/interrupted aortic arch continue to pose diagnostic challenges in the era of universal oxygen saturation screening. The former is likely to be addressed by slow and steady improvements in prenatal diagnosis, while this progress is much less likely with the latter. Very preliminary data suggest that PPI may provide added opportunity for CCHD detection, particularly with aortic arch anomalies. It is incumbent on programs using similar screening protocols to gather data and publish their experiences to further inform potential better practices for universal newborn oxygen saturation screening. Manufacturers of product lines relevant to this practice need to work closely with clinicians and health policy advocates to streamline informatics, data collection, and reporting to further inform optimal public health policy in universal oxygen saturation screening for newborns.

ACKNOWLEDGEMENTS. This article is dedicated to Jacqueline Anne Noonan, MD, and Abraham Rothman, MD, who inspired our interest in infant cardiology, and to Anne de-Wahl Granelli, PhD, who motivated our interest in universal oxygen saturation screening. Special thanks to families everywhere with infants affected by CHD, exemplified by Annamarie Saarinen and her team of mothers in the United States who advocated passionately and most effectively for the cause of universal oxygen saturation screening for infants with CCHD. Their passion continues to inspire us all.

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A 4-day-old female infant who was born at 39-weeks’-gestation comes to the emergency room with tachypnea, tachycardia, hepatomegaly, weak pulses, and very poor capillary refill time. Echocardiography shows hypoplastic left ventricle. Prostaglandin infusion is initiated, but the infant has a cardiac arrest and does not respond to resuscitative measures.

1. Which of the following is correct about detection of critical congenital heart disease (CCHD)?
   a. Data from several countries show that screening for CCHD using pulse oximetry is cost ineffective.
   b. Prenatal diagnosis results in 25%-50% detection of CCHD in the United States at the present time.
   c. Prenatal diagnosis results in 75%-90% detection of CCHD in the United States at the present time.
   d. The use of universal oxygen saturation screening as one of the newborn screening tests prior to discharge from hospital is not yet supported by evidence.
   e. Transposed great arteries, hypoplastic left heart, total anomalous pulmonary venous drainage, coarctation of the aorta, and interrupted aortic arch account for less than 30% of CCHD.

2. Advocacy for universal newborn screening for CCHD has its primary roots in which of the following?
   a. Academic research
   b. Government
   c. Industry
   d. Parent advocacy
   e. The lay press

3. Historically, the leading causes of death from CCHD are:
   a. Hypoplastic left heart and transposition of the great arteries
   b. Interrupted aortic arch and total anomalous pulmonary venous return
   c. Tricuspid atresia and coarctation of the aorta
   d. Truncus arteriosus and interrupted aortic arch
   e. Ventricular septal defect and Tetralogy of Fallot

4. According to the meta analysis cited by the authors, universal screening will:
   a. Include interrupted aortic arch or coarctation of the aorta as the majority of false-negatives
   b. Not be cost effective
   c. Not be useful in preterm infants
   d. Only be effective if applied after 24 hours after birth
   e. Pick up the majority of CCHD while missing up to 1 in 10 babies with disease

5. In terms of the method of postnatal screening, which of the following is correct?
   a. Direction of the difference in postductal and preductal saturations do not differ in terms of postnatal age.
   b. Functional saturation measures the oxyhemoglobin and reduced hemoglobin alone, and the fractional saturation measures the oxyhemoglobin, reduced hemoglobin, and approximates carboxyhemoglobin and methemoglobin. Hence, functional oxygen saturation tends to be 1.6 to 2 points higher than the fractional oxygen saturation.
   c. Peripheral perfusion index (PPI) relies on collection of a small quantity of venous and arterial blood.
   d. Postductal saturation measurements are clearly inferior to preductal.
   e. Preductal saturation measurements are considered standard of care for CCHD screening.
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