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Evaluation Of Pulse Oximetry As A Screen For Critical Congenital Heart Disease In Newborns

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Abstract

Evaluation of Pulse Oximetry as a Screen for Critical Congenital Heart Disease in Newborns. Rachel E. Klausner, Eugene D. Shapiro, Robert W. Elder, Eve Colson and Jaspreet Loyal. Department of Pediatrics, Yale University, School of Medicine, New Haven, CT.

The objective of this study was to report the results of and identify problems with a screening program using differential pulse oximetry (POx) to detect critical congenital heart disease (CCHD) in newborns. Charts of all infants born at four Yale New Haven Health hospitals in Connecticut between January 1 and December 31, 2014 were reviewed. Of 10,589 newborns, 171 (1.6%) underwent an echocardiogram before screening, 10,320 (97.5%) were screened by POx, and 98 (0.9%) were not screened. Of thirteen newborns (0.1%) diagnosed with CCHD, eleven (85%) were suspected of having CCHD on the basis of prenatal ultrasound, 1 (8%) was diagnosed due to clinical concern prior to screening, and 1 (8%) had a negative screening result but was subsequently diagnosed by echocardiogram following auscultation of a murmur. No infants with CCHD were identified through POx screening (POxS) alone. Four infants with a positive POx screen showed noncritical cardiac lesions by echocardiogram. The majority of infants were screened within the recommended 24 to 72 hours of life and had screens that were interpreted and documented correctly. Of 10,316 infants with negative POx screens, 52.1% remained in the Yale New Haven Health system at 1 year of age and no CCHD lesions were listed in their charts. Although a CCHD screening program was effectively implemented, perhaps due to high antenatal detection rates (85%), POxS did not lead to a substantial increase in the early identification of CCHDs in our hospital system.

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Introduction

Congenital heart disease (CHD) is the most common type of birth defect, with an estimated incidence of 8 to 9 cases per 1,000 births.[1-4] Approximately 25% of children with CHD have critical CHD (CCHD), a structural defect associated with significant risk of morbidity and mortality that requires surgical or catheter intervention before one year of age.[5,6] Prior to the widespread introduction of CCHD screening, it was estimated that up to one-third of infants with a potentially life threatening CCHD lesion left the hospital undiagnosed.[2,7-10] It has been shown that infants with CCHD who receive a delayed diagnosis have significantly higher mortality than those recognized prior to hospital discharge, with up to 40% presenting in cardiogenic shock and resulting in the deaths of 70-100 infants annually.[7,11,12] These data underscore the importance of early recognition of CCHD in neonates.

Pulse oximetry (POx) is a noninvasive painless test that estimates the percentage of oxygenated hemoglobin in the blood, and is now used as a screening test for CCHD.[5,13] The test is performed by comparing POx readings before and after the insertion of the ductus arteriosus into the aorta, typically on the right hand and either foot.[14] If the screening result is positive, an echocardiogram is performed as a confirmatory test.[5] POx screening (POxS) is expected to primarily detect lesions associated with hypoxemia due to right to left shunting of deoxygenated blood, such as hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, dextro-transposition of the great arteries, tricuspid atresia, and truncus arteriosus.[5,15] Other CCHD lesions have been established as secondary targets due to their less consistent association with hypoxemia, and thus less reliable detection rates by POxS.[5] These secondary targets

include coarctation of the aorta (CoA), double outlet right ventricle, Ebstein anomaly, interrupted aortic arch, severe pulmonary or tricuspid valve stenosis, and single ventricle complex.[5,15]

In September of 2011, following a recommendation by the Secretary's Advisory Committee on Heritable Disorders in Newborns, the US Secretary of Health and Human Services added POxS for CCHD to the Recommended Uniform Screening Panel for all newborns.[16] Subsequently, the American Academy of Pediatrics (AAP) endorsed this recommendation in December of 2011.[13] In May of 2012, the State of Connecticut passed legislation requiring hospitals to screen all infants for CCHD.[17] The legislation allows for individual hospital discretion over the type of testing to be used. CCHD screening results are not reportable to the Connecticut Department of Health, but hospitals may be audited in the event of a concern or during a routine onsite visit.[17] As a result of this mandatory legislation, a screening program was developed for CCHD for all newborns in the Yale New Haven Health (YNHH) system. As of 2014, this included infants born at Bridgeport Hospital, Greenwich Hospital and both the York Street and St. Raphael Campuses of Yale New Haven Hospital. The York Street Campus is the main academic hospital; the other three are community hospitals. The YNHH York Street Campus, Greenwich Hospital and Bridgeport Hospital have pediatric cardiology staff available. Infants born at the St. Raphael Campus who require specialist evaluation would be transferred to the York Street Campus, less than one mile away.

The YNHH screening protocol (Fig. 1) was adapted from an evidence-based algorithm proposed by the AAP, which is the basis for most screening protocols in newborns across the country.[13,18] Per our protocol, POx readings were taken in the right

Figure 1: YNHH CCHD screening algorithm adapted from the American Academy of Pediatrics.[18] R, right.

hand and one foot. A screening result is considered negative (pass) if an infant has ≥95% in either the right hand or one foot and a <4% difference between readings. These infants are considered low risk for CCHD, and thus receive normal newborn care. A positive screen (fail) is considered <90% in either the right hand or foot. These infants proceed to immediate evaluation by echocardiography. A screening result is considered borderline if the oxygen saturations in both the right hand and one foot are 90-94% or if there is a ≥4% difference between the two readings. These infants are re-evaluated in one hour. Three

consecutive borderline results are considered a failed screen, and these infants proceed to evaluation. It should be noted that the AAP algorithm is intended for use in screening full term infants in the well nursery.[18] However, due to state legislation and the lack of published guidelines, this protocol is used in our neonatal intensive care unit (NICU) as well.

In the YNHH CCHD screening protocol, CCHD screening is considered complete if the infant receives either POxS or an echocardiogram prior to hospital discharge. Infants are eligible for POxS once they are older than 24 hours of age and not receiving supplemental oxygen. It is recommended that POxS is performed after 24 hours of life to limit false positives associated with normal variation in blood oxygen levels during the newborn transition period.[5,8,19] It is also recommended that screening is performed prior to 72 hours to limit morbidity associated with delayed diagnosis of CCHD lesions.[8] This is particularly important for infants with lesions that depend on a patent ductus arteriosus to maintain pulmonary circulation, since closure of the ductus could result in circulatory collapse. For each infant who undergoes CCHD screening by POxS at YNHH, minimum documentation in the electronic medical record includes age at time of screening (hours), pre-ductal and post-ductal oxygen saturation (%), interpretation of the result (positive; negative; borderline, repeat in 1 hour), and follow-up of any positive or borderline result.

When the test is performed by comparing saturations between the right hand and either foot, POxS has been shown to have excellent specificity (0.05%) and moderate sensitivity, averaging around 76%.[20,21] The sensitivity of the screen has been shown to vary widely with the type of CCHD lesion (36-100%), with a substantial number of false-negatives occurring primarily among secondary targets of the screen.[7,14,20-22] Though the

false positive rate is low in term newborns, it has been shown to be higher in certain populations, including preterm infants and those born at high altitudes.[19,23-25] In addition, the rates of detection may vary with the proportion of infants with previously unidentified CCHD, suggesting that the incremental benefit of POxS may be lower in settings with higher antenatal detection rates.[6,26,27]

Screening with POx in asymptomatic newborns has been shown to reduce the diagnostic gap that is left by prenatal ultrasound and physical exam alone, and has been shown to increase early diagnosis of CCHD by up to 30%.[20,28-30] A recent study by Abouk et al. revealed that the implementation of mandatory screening has been associated with a 33.4% reduction in deaths due to critical congenital heart disease, translating to an absolute decline of 3.9 deaths per 100,000 births.[31] This increase in early detection has also been predicted to achieve diagnosis prior to significant physiologic compromise for an additional 900-1,100 infants per year.[20,32] Given that hypoxia and hypoperfusion associated with cardiovascular collapse have been associated with worse outcomes, POxS has the potential to reduce potential morbidity for hundreds of infants annually.[33,34]

Statement of Purpose

The purpose of this study was to report the results of and to evaluate problems with our screening program to detect CCHD in newborns. We sought to review existing literature and contribute additional data to the ongoing evaluation of our current screening protocol.

Specific Aims:

1. To report the results of the YNHH screening program, including the sensitivity and specificity of the POxS algorithm for CCHD lesions.
2. To describe issues with implementation of POxS at YNHH hospitals including number of infants not screened, lack of follow-up of positive POx screens, early and delayed screens, incorrect interpretation of POx results and inadequate documentation of results.
3. To review current literature regarding alternative algorithms, adaptations for special populations and additional methods of screening.
4. To review societal implications of widespread POxS, such as cost-effectiveness, psychosocial impacts and socioeconomic disparities.

Methods

The charts of infants delivered at Bridgeport Hospital, Greenwich Hospital, YNHH York Street Campus and YNHH St. Raphael Campus between January 1 and December 31, 2014 were reviewed. Data was collected from the YNHH electronic medical record system (EPIC®) with the assistance of the Yale New Haven Joint Data Analytics Team. Demographic information collected for each infant included patient name, medical record number, date of birth, gender, gestational age, birthweight, race, ethnicity, birth hospital and hospital unit. In addition, information regarding the presence or absence of an echocardiogram result, POxS data (result of screen, upper and lower extremity readings, differentials saturation and age at screen) and patient clinical problem lists from the electronic medical record were obtained. Individual patient charts were accessed on an as

needed basis for additional information. Liveborn infants who died before CCHD screening was performed were excluded.

We reviewed POxS data for all infants, including timing of the screen, presence of all data points, accuracy of interpretation and presence of appropriate follow-up, if indicated. Early and late screening was defined as screens performed before 24 hours of age or after 72 hours of age, respectively.[18] The charts of infants with negative POxS results were reviewed for any CCHD lesion diagnosed after hospital discharge. This was performed through review of the electronic medical record clinical problem lists for any cardiac lesion at the time of data collection, and again once all infants were greater than one year of age. In addition, we followed up infants to determine who remained in the Yale New Haven Health electronic medical record system as evidenced by primary care, subspecialty or emergency department visits in the first twelve months of life. Standard descriptive statistics were reported. The false positive rate was calculated by dividing the number of false positives by the number of negative samples (false positives plus true negatives), or as 1-specificity. The study was approved by the Yale Human Investigation Committee. The results of this study were published in 2017.[35]

Results

The characteristics of our study population are shown in Table 1. Eight live-born infants who died before CCHD screening could be performed were excluded. Of 10,589 newborns, 171 (1.6%) had an echocardiogram before POxS, 10,320 (97.5%) were screened by POx, and 98 (0.9%) did not undergo screening (Fig. 2). Of the 171 infants who received

Table 1: Subject Characteristics

	Hospital				
	Bridgeport Hospital	Greenwich Hospital	St. Raphael Campus	York Street Campus	Total
Infants, *n* (%)	2,403 (22.7)	2,645 (25.0)	909 (8.6)	4,632 (43.7)	10,589
Sex, *n* (%)					
Male	1,202 (50.0)	1,351 (51.1)	446 (49.1)	2,395 (51.7)	5,394 (51.0)
Female	1,201 (50.0)	1,294 (48.9)	463 (50.9)	2,237 (48.3)	5,195 (49.0)
Gestational Age, *n* (%)					
Term (>37 wks)	2,149 (89.4)	2,444 (92.4)	882 (97.0)	4,109 (88.7)	9,584 (90.5)
Late Preterm (35-37 wks)	140 (5.8)	126 (4.8)	26 (2.9)	267 (5.8)	559 (5.3)
Preterm (<35 wks)	114 (4.7)	75 (2.8)	1 (0.1)	256 (5.5)	446 (4.2)
Birthweight, *n* (%)					
AGA (2500-4000 g)	2,018 (84.0)	2,225 (84.1)	798 (87.8)	3,761 (81.2)	8,802 (83.0)
LGA (>4000 g)	183 (7.6)	263 (9.9)	83 (9.1)	451 (9.7)	980 (9.3)
SGA (<2500 g)	202 (8.4)	157 (5.9)	28 (3.1)	420 (9.1)	807 (7.6)
Screening Location, *n* (%)					
Nursery	2,176 (90.6)	2,389 (90.3)	857 (94.3)	4,062 (87.7)	9,484 (89.6)
NICU	227 (9.4)	256 (9.7)	52 (5.7)	505 (10.9)	1040 (9.8)
In-Patient Unit	0	0	0	65 (1.4)	65 (0.6)
Infant Race[A], *n* (%)					
White or Caucasian	954 (39.7)	1,619 (61.2)	208 (22.9)	2,775 (59.9)	5,556 (53.5)
Other[B]	753 (31.3)	352 (13.3)	348 (38.3)	712 (15.4)	2,165 (20.4)
Black or African American	536 (22.3)	117 (4.4)	293 (32.2)	696 (15.0)	1,642 (15.5)
Asian	43 (1.8)	138 (5.2)	7 (0.8)	291 (6.3)	479 (4.5)
Unknown	117 (4.9)	419 (15.8)	53 (5.8)	158 (3.4)	747 (7.1)
Infant Ethnicity[A], *n* (%)					
Non-Hispanic	1,517 (63.1)	1,957 (74.0)	523 (57.5)	3,847 (83.1)	7,844 (74.1)
Hispanic or Latino	827 (34.4)	317 (12.0)	376 (41.4)	691 (14.9)	2,211 (20.9)
Unknown	59 (2.5)	371 (14.0)	10 (1.1)	94 (2.0)	534 (5.0)

[A]Infant Race and Ethnicity were obtained from the medical record and are as self-reported by mother at time of admission to the hospital.
[B]Other includes Native Hawaiian or Other Pacific Islander, American Indian, or Alaska Native, as self-reported by mother.
Abbreviation: NICU, neonatal intensive care unit; SGA, small for gestational age; AGA appropriate for gestational age; LGA, large for gestational age

an echocardiogram prior to POxS, 40 (23.4%) did so due an abnormality detected on prenatal ultrasound and 131 (76.6%) had an abnormal postnatal finding.

Thirteen newborns (0.1%) were diagnosed with CCHD, resulting in an incidence of 1.2 per 1,000 infants in our population. All thirteen infants received an echocardiogram due to either an abnormal prenatal ultrasound (*n*=11; 85%) or auscultation of a heart murmur (*n*=2; 15%). The CCHD lesions of the 11 infants identified prenatally included hypoplastic left heart syndrome (*n*=3), tetralogy of Fallot (*n*=2), dextro-transposition of the great arteries (*n*=2), tricuspid atresia (*n*=1), double outlet right ventricle (*n*=2), and single ventricle complex (*n*=1). One of the infants who received an echocardiogram due to a heart murmur was evaluated prior to 24 hours of life and was found to have total anomalous pulmonary venous return. The other infant had a negative POxS result in the NICU on day of life 10, however a murmur was auscultated on day 13. A subsequent echocardiogram

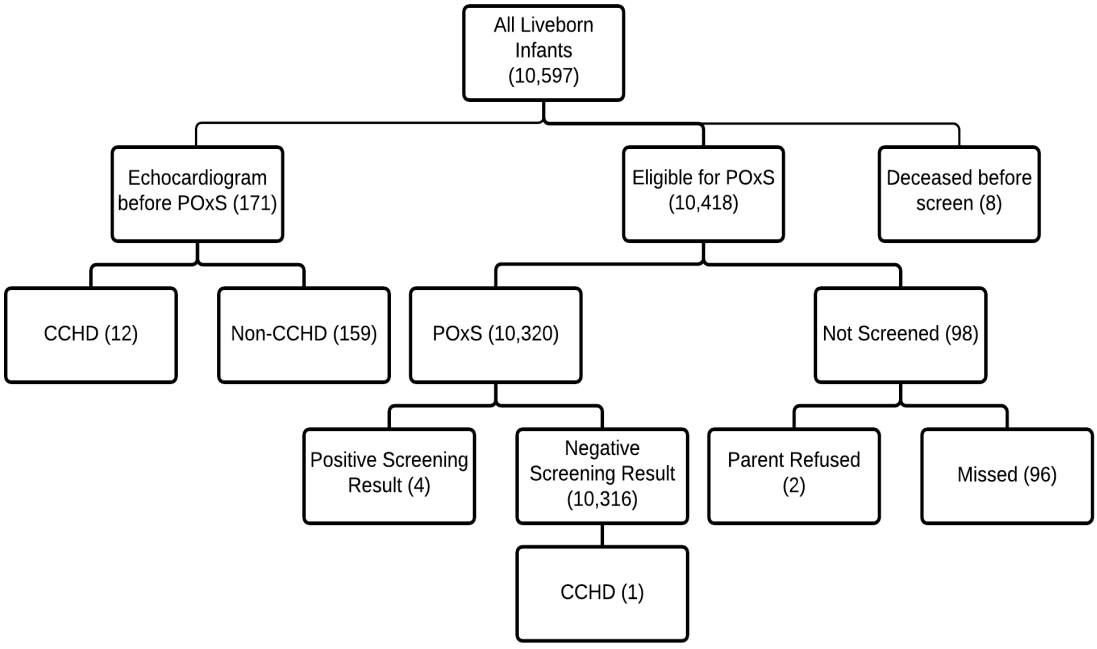

Figure 2: Results of the YNHH CCHD screening program.

Table 2: Infants with positive CCHD screening by POxS (*n*=4)

	Infant			
	1	2	3	4
Gestational age, wk	39 2/7	40 4/7	41 2/7	38
Birthweight, kg	4.14	4.43	3.32	3.33
Age at screening, h	25	27	31	24
Pre-ductal oxygen saturation, %	93	84	99	99
Post-ductal oxygen saturation,	100	95	89	86
Main Echocardiogram Findings	Small Atrial Septal Defect, Patent Ductus Arteriosus	Moderate-Large Atrial Septal Defect	Patent Foramen Ovale, Patent Ductus Arteriosus, Right Ventricle dilation	Moderate Tricuspid regurgitation, severely elevated Right Ventricle pressure

revealed CoA. For this newborn, although there was not an oxygen gradient on POxS (99% preductal and 100% postductal), the infant was noted to have decreased femoral pulses on physical examination and a >30 mmHg systolic blood pressure gradient (right upper extremity: 99/49; left upper extremity: 85/54; left lower extremity: 67/44; and right lower extremity: 63/42). Pediatric Cardiology believed this to be a critical cardiac lesion because the newborn required prostaglandin and, in the absence of early detection, could have presented in cardiogenic shock. The infant received surgical repair of the CoA at one month of life.

No infants with CCHD in our study were identified through POxS alone. Of 10,320 infants screened only by POx, only four infants (0.04%) had positive POxS results. All four of these infants were found to have non-critical CHD lesions on echocardiogram (Table 2), and subsequently had outpatient follow-up with pediatric cardiology.

Only 98 infants (0.9%) did not have CCHD screening documented before hospital discharge. Of these, 96 were not screened in error and two were not screened due to parent refusal. Seventy-five (78.1%) of the infants who were not screened in error were born at one of the community hospitals, with all but one (98.7%) occurring in the first eight months of 2014. Despite being unaware of the missed screens at the time, a documentation change made in the nursery of this hospital in September resulted in only one infant being missed for the remainder of the year. The other 21 infants (21.8%) who were missed were evenly distributed among the three hospitals. The demographics of the missed infants were not different than the overall study population.

Both cases of declined POxS were associated with refusal of the Hepatitis B vaccine by parents. One infant was an extremely preterm (gestational age <28 weeks) Non-Hispanic Black or African American female born at the main academic hospital. This infant's parents refused two-month vaccines while in the NICU as well. The other infant was a full-term Non-Hispanic White female born at a community hospital, whose parents also refused newborn metabolic screening and Vitamin K administration.

Of 10,316 infants with negative POxS at the time of birth, we reviewed post discharge records of 52.1% (*n*=5,367). None of these infants had evidence of CCHD at the time of record review. Six infants had died, and diagnosis at time of death was sudden unexpected infant death (*n*=4), complications from Otohara syndrome (*n*=1), and complications from spinal muscular atrophy type 1 (*n*=1). The infant with spinal muscular atrophy type 1 had a normal echocardiogram.

Of the 10,320 infants who underwent screening, 9,799 (94.9%) were screened

within the recommended window of 24 and 72 hours. Of the 521 infants (5.1%) who were screened outside of this window, 389 (74.7%) represented delayed screens (after 72 hours of life) and 132 (25.3%) were early screens (prior to 24 hours of life). The majority of infants with POxS completed after 72 hours of age had been admitted to the NICU (94.1%). The median age at screening for infants with delayed screens was 7 days, with a maximum of 104 days.

Incorrect interpretation of results (eg, screening results classified as normal when abnormal or vice versa) were uncommon (0.1%). Of 10,320 infants screened by POx, 6.5% (*n*=635) did not have all components of minimum documentation required in the YNHH protocol.

Discussion

More than 99% of newborns at our four hospitals were successfully screened for CCHD. Most CCHD lesions in our study population were detected prenatally, and no CCHD lesions were detected by POxS alone. The incidence of CCHD (1.2 per 1,000) is similar to that seen in other studies.[1,2]

False Positive Screens

Only 4 infants had positive POxS results, and all were found to have non-critical CHD lesions (Table 2). The rate of false positive results (0.04%) is similar to the false-positive rate of 0.05% reported in newborns screened after 24 hours of life,[26] which is when screening was performed in our program. Screening after 24 hours has been widely accepted in the United States to limit false positive results associated with earlier screening,

thereby limiting the number of unnecessary echocardiograms and preventing undue burden on clinical referral staff.[36-38] However, this must be balanced with the risk of infants with CCHD becoming symptomatic prior to screening.[34,39] Given our low rate of previously undiagnosed infants with CCHD, only one infant in our study group was symptomatic with a murmur prior to POxS. In larger studies, however, half of previously unidentified infants with CCHD were found to exhibit symptoms before 24 hours of life, with 10% presenting in acute cardiovascular collapse.[7,30]

Although none of the infants with a positive POxS had CCHD in our study, all 4 did have CHD. There are potential benefits of POxS in early identification of non-critical yet clinically important lesions such as septal defects, allowing for appropriate referral and follow-up. In addition, it should be noted that all false positive screens represent infants with low oxygen saturations that warrant further evaluation.[33] Previous studies have shown that 27-67% of false positive screens were due to other significant pathology, allowing for early diagnosis and intervention of clinically relevant conditions such as pneumonia, pulmonary hypertension and sepsis.[37,40-43] Widespread surveillance and reporting of both non-critical CHD lesions and serious non-cardiac conditions detected by POxS will provide additional information that may expand the list of conditions targeted by POxS.[44,45]

Alternatives to the AAP Pulse Oximetry Algorithm

Two alternatives to the AAP-endorsed algorithm for POxS have been proposed, with the intent of optimizing sensitivity and/or efficiency for screening in full term newborns. The New Jersey Department of Health POxS algorithm (Fig. 4) requires an oxygen saturation >95% in both the right hand and one foot and a <3% difference between

the two extremities to pass with first measurement.[15] This is a higher threshold than the AAP algorithm, where a >95% saturation in either the right hand or one foot is accepted to fulfill the criteria.[5] With this slight modification, the New Jersey algorithm proceeds similarly to the AAP with regards to borderline and failed screens.[15] The New Jersey protocol has been shown to have higher sensitivity for detecting CCHD lesions, but also a higher rate of false positive screens.[46]

Tennessee has recently proposed a new staged approach that would first test a POx reading at a postductal site (one foot), and only proceed to a preductal reading if the result

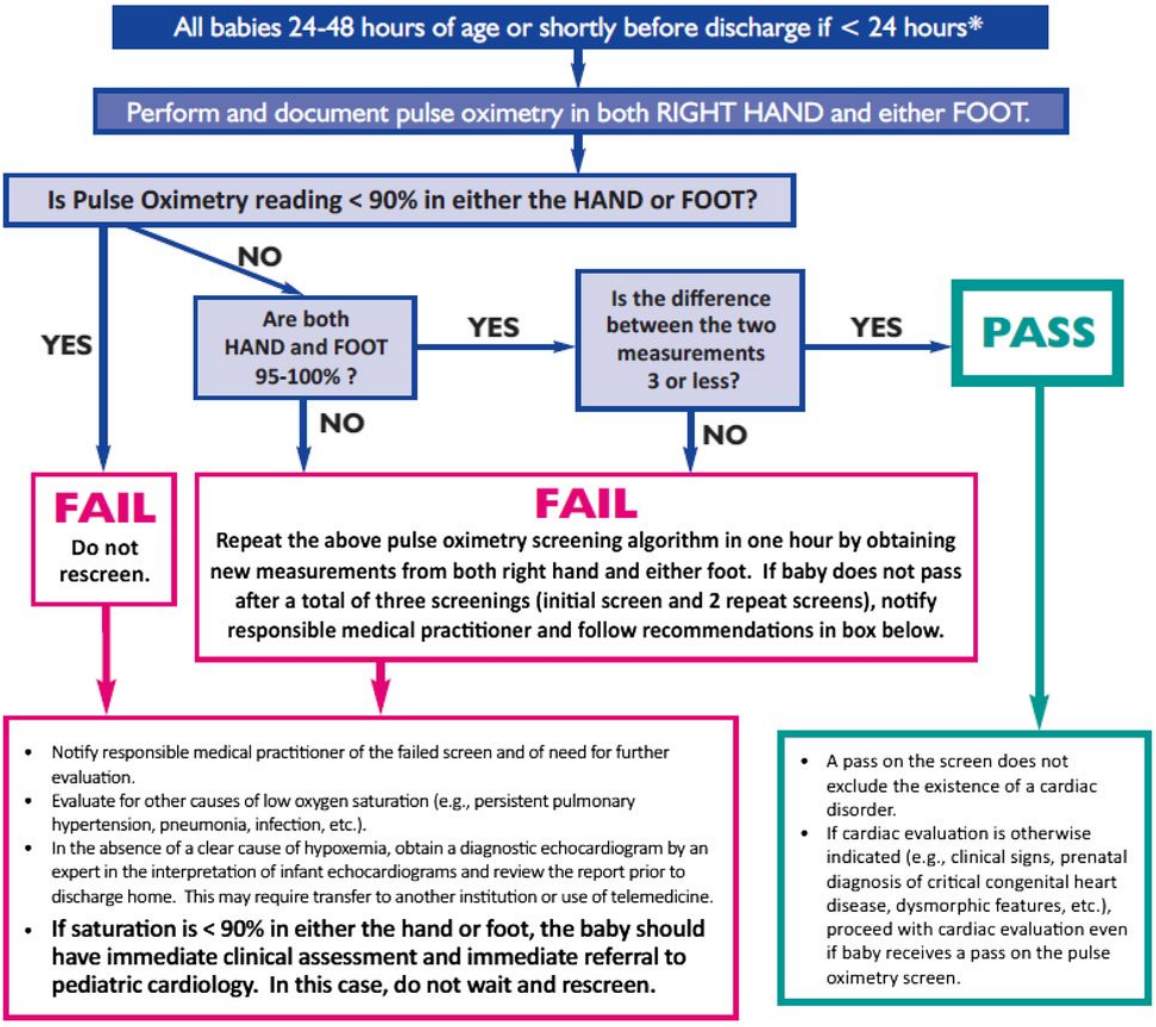

Figure 4: New Jersey Department of Health POxS Algorithm[15]

is indeterminate.[47] Per the Tennessee Algorithm (Fig. 5), an oxygen saturation in the foot ≥97% is considered a pass, and a reading <90% is considered a fail. If the reading is 90-96%, the right hand is then tested and the infant would default to the AAP algorithm.[47] Previous studies have questioned the benefit of measuring preductal saturation reading, suggesting that a postductal reading alone may be sufficient.[22] Physiologically, the postductal site would be expected to have a lower saturation than the preductal site in nearly all cases. The one exception is transposition of the great arteries, where a reversal of saturations (postductal > preductal) could be seen. Though rare, there have been reported cases of transposition associated with unexpectedly high postductal saturations (96-97%) sufficient to affect the sensitivity of the screen.[22,37,40] When compared to the AAP and New Jersey algorithms, it has been shown that the proposed Tennessee modifications resulted in the lowest sensitivity, but also the lowest false positive rate.[46]

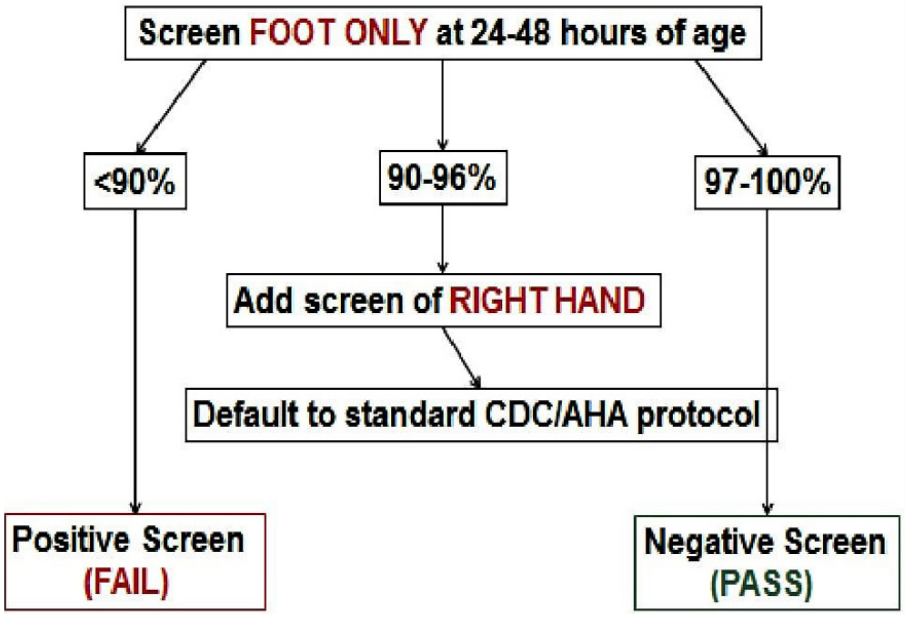

Figure 5: Tennessee Modified POxS Algorithm[47]

Additional Methods of Screening: Blood Pressure Differentials

The infant in our study who was diagnosed with CoA after a negative POxS result is an important reminder of the limitations of POxS for certain CCHD lesions, particularly those deemed secondary targets of the screen. CoA, a narrowing of the descending aorta near the insertion of the ductus arteriosus distal to the left subclavian artery, results in a limitation of blood flow to the lower extremities. Patients with CoA have a variable presentation dependent on the location of narrowing, severity of flow limitation and patency of the ductus arteriosus. Lower extremity hypoxemia may be seen with severe preductal coarctation, where the only flow to the lower extremities originates from the pulmonary artery through the ductus arteriosus. However, in less severe cases or those where the narrowing occurs at or after the insertion of the ductus, limitation of flow does not necessarily correlate with reduced oxygen saturations. This inconsistent association with hypoxemia results in low sensitivity of POxS for these lesions.

A study by Schultz et al. found that over 90% of cases of significant physiologic compromise deemed to be potentially preventable by earlier diagnosis were due to aortic arch obstruction; the authors argue that any viable screening strategy must be sensitive for such lesions.[48] Two methods have been proposed as complements to POxS to in an attempt to increase the sensitivity for lesions such as CoA and interrupted aortic arch, including screening for differential blood pressure or and the measurement of peripheral perfusion indices.

Upper-to-lower extremity blood pressure differentials have widely been used as a useful diagnostic tool for CoA in older children, and was shown to be more reliable than

absent or decreased lower extremity pulses.[49] Despite this, the utility as a screening method for aortic arch abnormalities in infants was previously unclear.[50] Patankar et al. performed a retrospective case-control study comparing four extremity blood pressure measurements in infants upon admission to the NICU.[50] Similar to our infant with CoA, a significant upper extremity to lower extremity blood pressure differential did exist at birth in cases subsequently diagnosed with aortic arch anomalies. However there was significant overlap with controls, resulting in low specificity.[50]

Boelke et al. investigated the utility of pre and postductal blood pressure measurements in addition to POxS for the detection of CoA in infants.[51] A blood pressure gradient of >15 mmHg was repeated in two hours, and if persisted, the infant was referred for evaluation. During the study period, no infants with CCHD were identified through blood pressure or POxS, and abnormal blood pressure measurements were responsible for the majority of improperly completed screenings, repeat screening and false-positive screening. The addition of blood pressure measurements was found to increase the false-positive rate to 0.13% from 0.01% with POxS alone.[51] This is consistent with previous studies showing a wide variability in blood pressures between extremities in healthy neonates, up to 20 mmHg.[52] Given the difficulty of obtaining accurate blood pressure measurements in neonates, the high false positive rates and smaller target population, blood pressure readings appear to lack utility as a widespread screening tool.[51]

Additional Methods of Screening: Peripheral Perfusion Index

The measurement of the peripheral perfusion index (PPI) in addition to POxS was proposed as a method to increase the sensitivity for detection of not only aortic arch

anomalies, but also other left ventricular outflow obstructive defects such as critical aortic stenosis and hypoplastic left heart.[53,54] PPI is a measurement of the relative amount of arterial perfusion, reflecting real-time changes in peripheral blood flow.[54] This measurement is derived from a pulse oximeter and is calculated as the ratio of the pulsatile to non-pulsatile component of infrared light reaching the sensor.[55] As measured, the PPI would be expected to be decreased in left heart obstructive lesions, as well as other causes of systemic hypoperfusion such as sepsis.[54] Given that the PPI is derived from the pulse oximeter already used for POxS, its use would not expected to additionally burden the clinical staff responsible for performing newborn screening.[53]

A prospective case-control study in Sweden measured pre and postductal PPI of 10,000 newborns, including nine with left heart obstructive defects.[54] This study established that a PPI value below 0.70 (<5th percentile) indicates potential left heart obstruction (OR 23.75), and that a value less than 0.50 (<1st percentile) indicates definite hypoperfusion.[54] Of the nine infants with left heart obstructive defects, five had PPI below 0.70, and all had measurements below the inter-quartile range (<1.00). Two of the infants with abnormal PPI, who were subsequently diagnosed with CoA and hypoplastic left heart syndrome, respectively, had been unrecognized following physical exam and POxS.[54] As a result, the addition of PPI to routine screening practices in this study increased the detection rate from 77.8% to 100%.[54]

A more recent investigation by Schena et al. of over 40,000 infants in Italy showed less promising results, despite using a higher PPI cutoff (<0.9) expected to increase sensitivity.[53] Though the addition of PPI resulted in the detection of one additional case of CoA that had been missed by physical exam and POxS, two cases went undiagnosed prior

to discharge. Their false positive rate was found to be 0.27%, which is higher than is commonly seen with our current POxS algorithm.[26,53]

The addition of PPI to POxS has the potential to increased detection rates for left heart obstructive lesions, but may lead to an increased number of false positive screening results given the wide distribution of PPI in the normal newborn population and variation with factors such as skin temperature.[53,54,56] As our infant with CoA was noted to have decreased femoral pulses on exam, we postulate that this infant would have benefited from PPI screening. However, further investigations of PPI would need to be undertaken to establish an optimal screening algorithm prior to its widespread incorporation into current screening practices.

Clinicians must continue to maintain a high index of suspicion for lesions such as CoA that have been shown to have low detection rates by POxS, and are also the most likely to be missed by prenatal ultrasound and newborn exam.[7,14,20,57,58] Even with the addition of further methods of screening such as PPI, cases of CCHD can still be missed.[53] This reinforces that, unfortunately, no current method of screening can reduce the diagnostic gap completely to ensure that all infants are diagnosed prior to discharge from the hospital.[39]

Implementation of POxS

For the majority of infants who underwent POxS in our study, screening was completed as recommended with few missed screens and appropriate follow-up of positive screens. In most instances, all components of POxS results (age at time of screening [hours], pre- and postductal oxygen saturation [%], interpretation of the result [positive;

negative; borderline, repeat in 1 hour], and follow-up of any positive or borderline result) were documented. Though not directly assessed in our study, POxS has previously been shown as posing minimal additional burden to nursing staff, requiring an average of 5.5-9 minutes per infant.[45,59-61]

Despite the success of our screening program at YNHH, providers should be aware that POxS presents clinical challenges in its implementation. Unlike metabolic newborn screening performed through a dried blood spot, POxS screening requires a medical professional not only to perform the test, but also to correctly interpret and document the results.[44,45,62] Reporting the results of POxS in a useful format for clinicians is more complex than those of hearing or metabolic screening. It is important that oxygen saturations are recorded and interpreted correctly, as the results have the potential to affect immediate clinical decision making. Though misinterpretation of the algorithm was uncommon, it did occur, reinforcing the need for thorough training of screening staff. Others have proposed quality improvement measures such as an automated alert in the electronic medical record for saturation values outside of the protocol threshold to reduce misinterpretation.[45] Unlike screening for congenital hearing loss, for which evaluation can be delayed weeks without significant long term consequence, newborns with a positive CCHD screen require immediate evaluation by a pediatric cardiologist.[44]

Screening in Special Populations: Neonatal ICU

The AAP POxS algorithm was originally designed for screening of full-term infants in the well-baby nursery. This has resulted in uncertainty regarding the expansion of POxS to the estimated 8-12% of infants admitted to the NICU annually, particularly for premature

infants and/or those with supplemental oxygen requirements.[19,63] Whereas low-risk infants in the newborn nursery, with their shorter hospital stays and less intensive evaluations, have been shown to benefit from POxS, the incremental benefit of CCHD screening in the NICU is unclear. Some have argued that standard-of-care monitoring of infants in the NICU is often sufficient to exclude or confirm CCHD given the extended stay, frequent physical exams and continuous pulse oximetry.[28,44,64] In addition, many of these infants receive additional investigations such as chest x-rays and echocardiograms during their stay, the sum of which would be expected to alert providers to the presence of a CCHD lesion.[28] Given this, the target population of otherwise undiagnosed NICU infants with CCHD is likely very small, resulting in a much larger number needed to screen than infants in the well nursery.[28] The actual true positive rate of screening in the NICU is not known at this time, nor is the cost per additional infant detected.[19]

Despite those who argue that screening in the NICU is of little benefit, concerns have been expressed about this generalization leading to missed opportunities for early detection given different levels of NICU care and the large number of infants who approximate the well newborn population.[24,63] Van Naarden et al. found that nearly half of the infants in their NICU population were demographically similar to the well-baby population (>2500 g, >37 weeks) and that >70% were not on oxygen at 24 hours, suggesting that standard screening may be of benefit.[24] In addition, particular circumstances have been noted where infants could be missed despite routine NICU monitoring: infants without a fetal or postnatal echocardiogram, infants for whom an echocardiogram is obtained for the evaluation of a patent ductus arteriosus but not all structural malformations, or infants with low oxygen saturations limited to a limb where

the pulse oximeter is not placed.[28]

The current algorithm, including cutoff parameters and optimal screening window, was developed in reference to full term neonatal physiology.[13] While we did not find any false positives amongst our NICU infants, other studies have shown that screening preterm infants <35 weeks gestation results in more positive screens in infants without critical cardiac disease, and that this false positive rate is often directly correlated with the degree of prematurity.[23,24] Though it has been estimated that up to one-third of infants receive echocardiography in the NICU for other reasons,[19,65,66] a significantly increased false positive rate like that found by Hu et al. would result in hundreds of unnecessary echocardiograms, cardiologist consultations and heightened parental anxiety.[23,67]

Given that the POxS is based on the measurement of blood oxygen saturations, it is standard practice to only screen infants on room air. For infants receiving supplemental oxygen, there is thought to be an increased risk of both false negative screens, due to oxygen therapy masking low saturations, and false positive screens, with infants requiring oxygen for non-cardiac disease.[28] The vast majority of screens performed after 72 hours of life in our study occurred in infants who had been admitted to the NICU, likely due to the high rates of supplemental oxygen requirements among these infants and the need to wean prior to screening. Goetz et al. found similar results in their NICU population, with 67.4% of infants with delayed screens due to oxygen requirements, and many being screened after CCHD would have been expected to be symptomatic.[64] With current screening practices, it has been thought reasonable to obtain an echocardiogram (if one has not previously been done) for infants being discharged home from the NICU on oxygen.[66]

For infants receiving supplemental oxygen, a two-staged screening protocol has been proposed (Fig. 6)[24] to increase early detection while minimizing false positive results. This modified algorithm includes an initial screen while on oxygen during the AAP recommended window, with a second screen being performed after weaning to room air.[24] An additional modification included categorizing infants with saturations <95% but a differential saturation <4% as "conditional passes", and only rescreening for a differential of >4%. Using this modified algorithm, 2.1% of infants receiving supplemental oxygen failed the screen, compared to 25.9% had these infants been screened with the standard algorithm. However, in this study, no additional infants with CCHD were identified due to the screen and all of the failed screens represented false positives. Despite the reduction

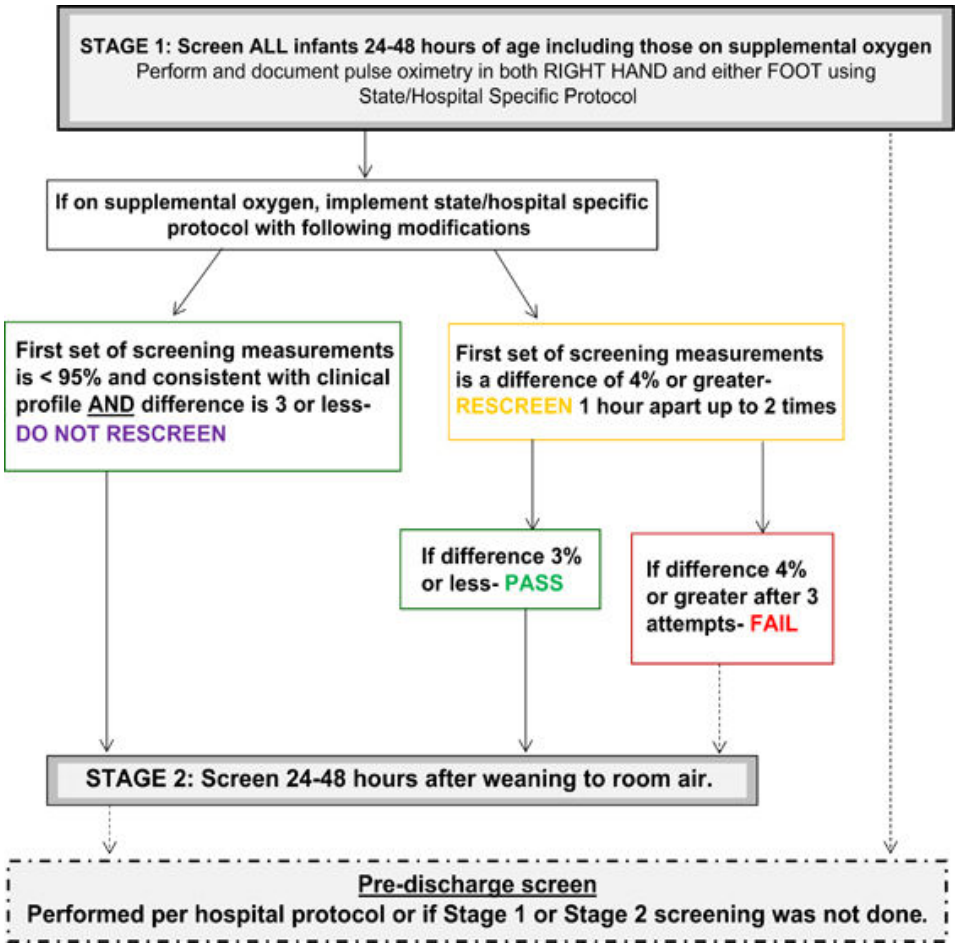

Figure 6: Multi-staged Algorithm for Screening of NICU Infants[24]

achieved using the modified algorithm, this false positive rate for infants on oxygen is still significantly higher than was seen with infants on room air (0.5%).[24] When the infants were screened immediately after weaning from oxygen, the false positive rate was similar to those infants on room air (0.6%),[24] however the utility of delayed screens for early detection of CCHD at this time is unclear. It is worth noting that all infants with CCHD in this study, including those not identified prenatally, were symptomatic prior to screening with either desaturations, tachypnea and/or an audible murmur.[24]

Due to the legislation passed in Connecticut, all newborns are screened for CCHD prior to discharge regardless of clinical status during the recommended screening window.[17] In other states, however, the lack of specification of the current AAP algorithm for NICU populations and the concerns of high false positive rates have led to wide variations in screening practices among hospitals.[24,28,44] Further investigation of POxS for infants in the NICU will involve the determination of an optimal screening protocol that would optimize early detection while minimizing the false positive rate.

Screening in Special Populations: High Altitude

The AAP and others have long recognized the need for adaptation of the POxS protocol for use at elevation, with the concern that use of the current saturation cutoffs would negatively affect the specificity and result in excessive and unnecessary interventions.[5,18,68,69] In addition to typical high-altitude hypoxia seen in children and adults, two other mechanism are thought to contribute to lower saturations observed in newborns at elevation. The lower atmospheric pressure of oxygen is thought to lead to a delay in the normal transition from fetal to newborn circulation through persistently

increased pulmonary vascular resistance, leading to more right to left shunting at the level of the ductus arteriosus and foramen ovale.[25,70] This may be compounded by limited respirations following birth due to the delayed maturation of the respiratory center.[70] As a result, healthy infants born at elevation >1500 m have lower systemic oxygen saturations compared to infants at sea level, with mean pulse oximetry readings ranging 91-96%.[68,71-74] Contrastingly, two studies concluded that POxS is reasonable at mild altitude (<800 m) with minimal variation in oxygen saturations compared to sea level.[75,76]

Wright et al. were among the first to publish the results of a screening program above 1500 m at their site in Aurora, Colorado.[25] As expected, the authors found an elevated false positive rate (0.75-1.1%) with the standard algorithm, with the true rate possibly being as high as 2.7% when accounting for incomplete screens.[25,77] The group in Colorado has proposed two alternatives to the AAP screening algorithm, adapted for use at elevation. In the first algorithm (Fig. 7), any infant with saturations <85% is classified as having failed, as are infants with saturations <90% or a differential >3% that persisted after three screenings. This lower threshold is thought to prevent false positives in normal newborns at altitude, though no data has been published regarding its sensitivity and specificity.[25] A subsequent proposed algorithm involved placing 'borderline' infants (those with saturations between 86-94% or >3% difference) in an oxygen hood designed to replicate sea level atmospheric oxygen tension to accelerate neonatal transition, then testing up to two additional times using the standard AAP protocol.[77] The use of this second algorithm resulted in a failure rate of 0.3%, which is more comparable to that found at sea level.[77] Though these results may be promising, further investigations will need to be undertaken before any alternative practice can be widespread.

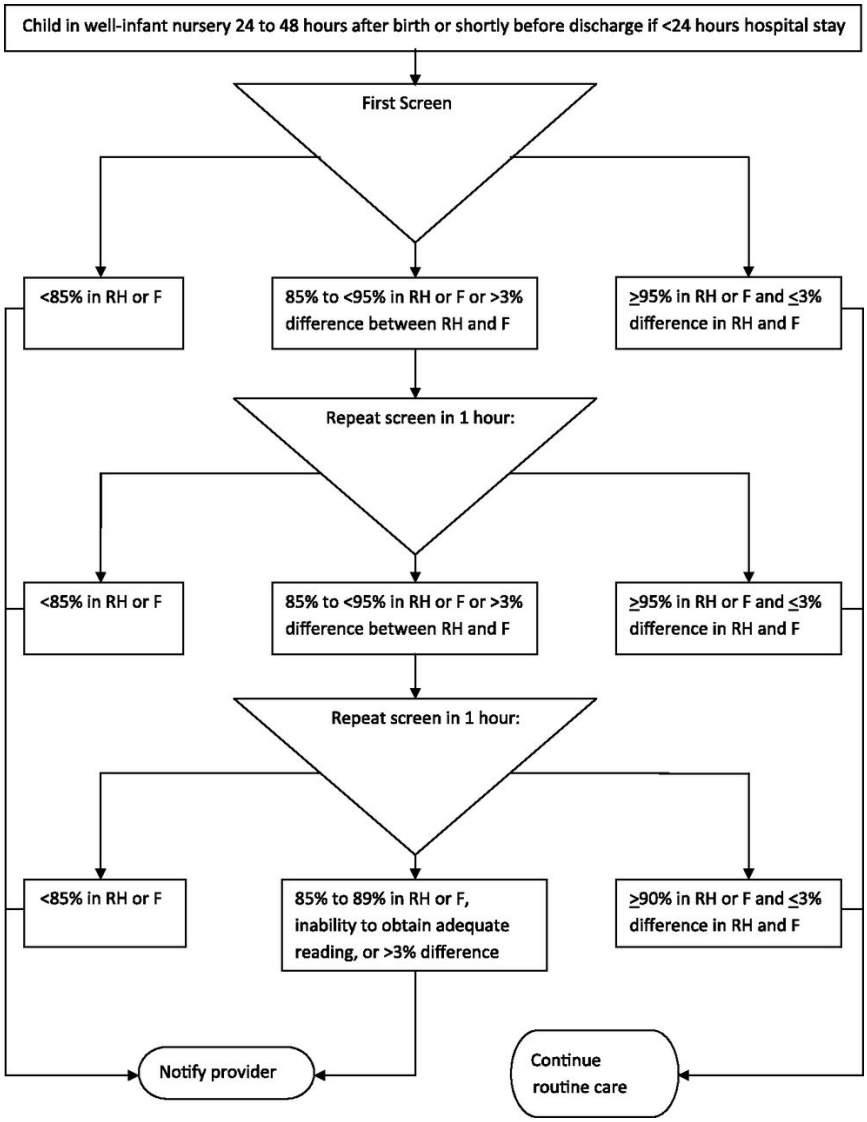

Figure 7: Modified Algorithm for Screening at Elevation[25]

Screening in Special Populations: Low Resource Settings

Due to a high percentage of antenatal detection in our tertiary care academic center (85%), POxS may not lead to a substantial increase in the early identification of CCHD in our population. However, broad geographic and hospital-level variation has been documented for both rates of prenatal diagnosis and timely detection.[78,79] As a result, the

impact of CCHD screening may be more pronounced in community hospitals or other settings in which the rates of antenatal detection by ultrasound is relatively low.[26,27,39,59,80] Within the United States, POx has been successfully used in the evaluation of infants in states such as Wisconsin, Washington and Minnesota with lower rates of prenatal ultrasound and higher rates of births outside of specialty centers, including out-of-hospital births.[41,45,81,82]

Narayen et al. proposed an alternative screening protocol for use in planned out-of-hospital births, in an attempt to accommodate time constraints of community based midwives in the Netherlands.[83] This adapted protocol implements an initial POx measurement on soon after birth with a second screen at the first follow-up appointment on day two or three of life, and was shown to have a modestly increased false positive rate (1.0%).[43,83] Given that infants born at home do not receive the same level of routine monitoring immediately after birth, implementation of POxS in homebirths has the potential to increase safety through the detection of not only CCHD, but also non-critical CHD and other non-cardiac pathology.[43,83] In addition, this protocol could be adapted for use in early hospital discharges (before 24 hours of life). Despite the potential benefits, there is limited evidence of the efficacy of the proposed protocol and further investigations will need to be carried out before this variation could become standard practice.

There are significant barriers that exist to implementation of POxS in lower resource settings, including obtaining portable pulse oximetry equipment and training of community practitioners in POxS technique and interpretation.[82,83] The logistics of appropriate follow up for infants with positive screens presents an additional challenge, including neonatal echocardiographers and pediatric cardiology staff for advanced

diagnosis and management. In addition, access to basic but time sensitive resources, such as prostaglandin for acute stabilization through maintenance of pulmonary blood flow in ductal dependent lesions, can often times be limited at local and regional hospitals.[45,82,83] A study from Washington state showed that as long as initial stabilization is performed in a timely manner, birth hospital location and need for transport to a tertiary care center does not affect mortality from CCHD, reinforcing the importance of early recognition and intervention.[81] An additional ethical dilemma presented when considering the use of POxS outside of the United States is the availability of palliative or corrective surgery, since pediatric cardiothoracic surgeons, anesthesiologists and intensive care may not be widely available in developing countries.[84] Thus, if communities are able to ensure practitioner access to prostaglandin, it is reasonable to conclude that increased early detection of ductal-dependent cardiac lesions through the successful implementation of POxS could improve neonatal mortality from CCHD in communities within the United States. However, improved infrastructure is likely required before a similar effect could be seen in certain lower resource countries.

Cost-effectiveness of POxS

Based on current data available, CCHD screening in the United States has been widely accepted as cost-effective.[32,60] The total average cost of POxS has been estimated at $6.28-$14.19 per newborn factoring in the cost of equipment, labor and further investigations for positive screens.[32,60] Although there have been concerns about the rates of false positive screening results, the cost of unnecessary echocardiograms in these infants has been shown to have a minimal impact on overall cost.[32] Peterson et al. calculated based on the Florida Birth Defects Registry that among infants with CCHD, those whose defects

were detected after hospital discharge spent an average of 18% more days hospitalized during the first year of life than those who were with timely diagnoses.[32] The cost associated with these additional days of inpatient care could potentially be negated by widespread screening.

In their paper, Mouledoux et al. states that the Tennessee two stage approach (Fig. 5, pg. 13), which involves an initial postductal-only reading with default to the AAP algorithm if indeterminate, is more efficient than the currently established practice in terms of cost and time to perform the screen. Using previous cost estimates, the authors argued that this alternate algorithm would eliminate up to 3.8 million unnecessary pulse oximetry readings each year and amount to a savings of approximately six million dollars.[32,47] The authors did note, however, that the upfront cost associated with retraining staff with the new algorithm nationwide may negate these savings.[47]

Overall, the currently established practice has been deemed to be cost-effective on a national level. It should be noted, however, that these studies were conducted regarding full term well newborns. No population level evidence currently exists regarding the additional cost burden of false positives associated with screening of infants born preterm or at high altitude. Despite the large number of states that have active legislation or are undergoing trials of CCHD screening (48 as of 2016, see Fig 8),[85,86] there has been difficulty accumulating screening data due to a lack of standardized collection or analysis.[11,85,87] Though the AAP-endorsed algorithm is the nationally recognized standard, this algorithm is not used exclusively across screening programs,[13,18] complicating a comprehensive surveillance program that would likely be required for ongoing quality improvement and algorithm adaptation. Ideally, centralized data collection would include

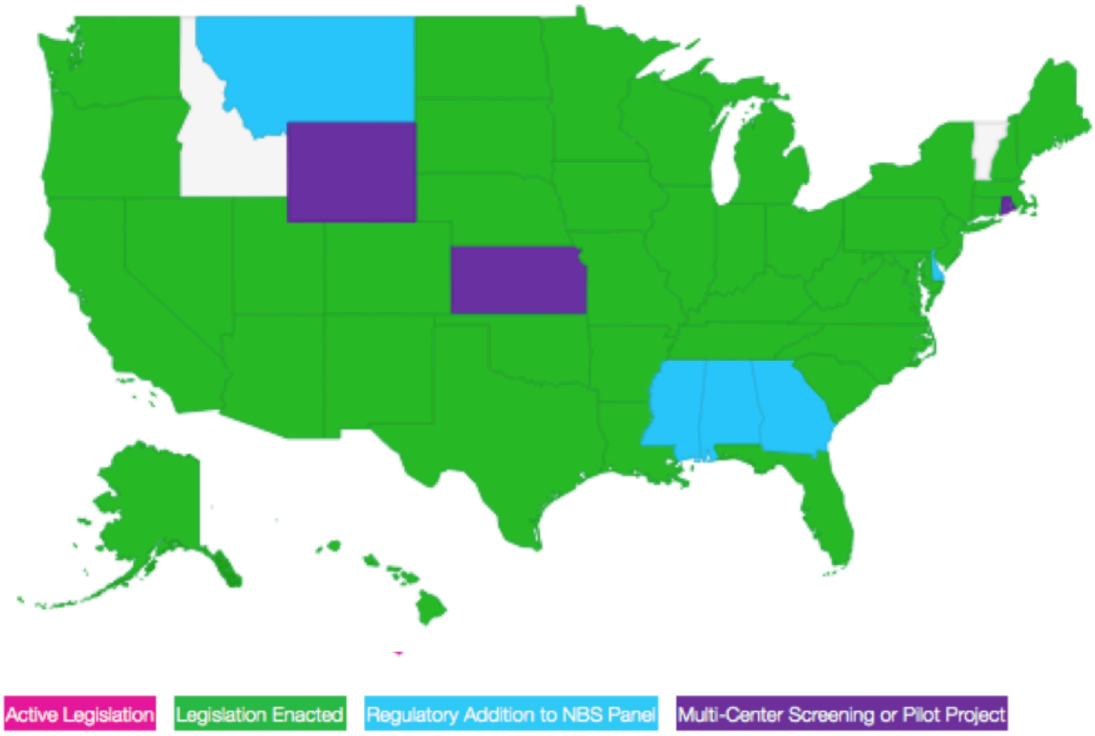

Figure 8: CCHD Screening Map[47]

not only immediate screening and results of false positive screens, but also follow-up for false negative screens and for the assessment of long-term outcomes.[88,80] In addition, it will be important to continue to reassess the cost effectiveness of screening in different hospitals, such as those with different methods of implementation or rates antenatal detection of CCHD.[32]

Psychosocial Impact of False Positives

Though less of a concern when screening well newborns due to the high specificity, there exists a potential negative psychosocial impact of the large number of additional false positives in screening infants in the NICU or at high altitude.[25] Though studies have shown a heightened parental stress levels associated with false positive metabolic screening results,[89-91] the data that currently exist regarding parental responses to false positive results

in CCHD screening suggest minimal additional anxiety.[92] This study was conducted at a large academic center in the United Kingdom, however, and may not take into account the potential delay associated with obtaining a confirmatory echocardiogram (for example, if a transfer of hospitals is required). In this situation, similar levels of distress may be expected to those seen in parents awaiting confirmatory testing for infants suspected of having cystic fibrosis.[93] When developing an optimal screening protocol for these special populations, psychosocial impact on parents should be considered with an increased number of false positive screens, in addition to concerns regarding increased cost and staff burden.

Socioeconomic Disparities

Consistent with the low opt-out rate seen in our study, it has been shown that POxS has been widely accepted by parents, who generally recognize POxS as an important test to detect ill infants.[38,62,92,94] In our population, refusal of CCHD screening by parents appears to be more associated with refusal of other standard-of-care medical practices, such as vaccine administration and metabolic screening, than with race, ethnicity or socioeconomic status. Despite this, Powell et al. showed significant disparities in refusal rates among ethnic groups, with Black/African mothers declining 4.5 times more often than White mothers.[92] This study also revealed that non-White mothers were significantly more anxious and less satisfied regarding the test.[92] Though the reasons for this are unclear, identification of factors leading to differences in participation and satisfaction among ethnic groups would allow staff is better able to educate and support these parents.[92]

Though an association between ethnicity, delayed diagnosis and increased mortality has been shown in other countries,[95] it is unclear how much delayed diagnosis is contributing to these disparities within the United States. Prenatal detection rates are thought to be lower among infants born to Black or Hispanic women,[78,96] but no significant differences have been found in age at first postnatal echocardiography or age at referral to pediatric cardiac care.[97,98] Nevertheless, previous studies have shown a significant difference in early childhood mortality from certain CCHD lesions among different racial groups, with increased risk of death in Hispanic and non-Hispanic black children when compared to non-Hispanic whites.[97,99-101] It has been suggested that this difference in mortality could be related to a number of other factors, including differences in defect severity, home care and non-cardiac causes of death.[100] Though POxS has the potential to increase early diagnosis in populations with lower rates of prenatal screening, no studies exist to support or refute whether significant decreases in the mortality gap among ethnic groups could be attainable through POxS. As more data on the results of screening becomes available at a population level, further research should be conducted to investigate the acceptability and impact, if any, of POxS among ethnic groups within the Unites States since its widespread implementation.

Limitations

There are some limitations to our study. We were able to conduct longer-term follow-up to see if CCHD was detected in any of the infants in only approximately half of the newborns, as many did not have records of subsequent visits in the YNHH system through one year of age. The possibility exists that an infant with a false negative screen was diagnosed with CCHD and treated outside of our hospital system. However, it is likely

that most would have returned to our hospital system if CCHD had been diagnosed, given that many of whom would be seeing their own pediatricians in the immediate area. Of six infants who died, four deaths were due to sudden unexpected infant death. In discussions with physicians directly involved with these four cases, the deaths were all attributed to unsafe sleep conditions. Given that this was a retrospective study, the type of pulse oximeter used was not standardized, and it is unknown whether the manufacturer and model used were consistent between hospitals and units. Demographic markers of socioeconomic status such as insurance type were not collected; this information could have assisted in the further characterization of our study population. The number of infants screened in the one-year time period over which data was collected may have been insufficient to detect a noticeable effect. Given that more time has passed since the state-wide initiation of CCHD screening in Connecticut, additional studies could be conducted to further investigate the impact.

Conclusions

We successfully implemented CCHD screening in our large tertiary care hospital system in response to legislation enacted by the state of Connecticut. Although no infants with previously unrecognized CCHD were detected in our four YNHH hospitals during the study time period, recent data has shown that the enactment of mandatory screening is associated with a significant decreased rate of infant deaths from CHD, suggesting that infants in other states could benefit from such policies. Though a substantial amount of research exists on the use of POx as a beneficial screening tool, many questions remain unanswered regarding optimal implementation with the ultimate goal of increasing early detection of CCHD.

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