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Short title (running head): Algorithms for Newborn Pulse Oximetry Screening

Andrew K Ewer,[1,2] Gerard R Martin[3]

Affiliations

1. Department of Neonatology
    Birmingham Women's Hospital NHS Trust
    Birmingham
    B15 2TG
    UK

2. Institute of Metabolism and Systems Research
    College of Medical and Dental Sciences
    University of Birmingham
    Birmingham
    B15 2TT
    UK

3. Children's National Health System
    Washington DC
    USA

Address for correspondence: Professor A K Ewer, Neonatal Unit, Birmingham Women's Hospital, Edgbaston, Birmingham UK. B15 2TG. Email: a.k.ewer@bham.ac.uk

Abbreviations: POS – Pulse Oximetry screening, CCHD – Critical congenital heart defect

Contributor's statements: Both authors discussed the contents initially, AKE wrote the first draft and edited the final draft. GRM provided further comments and edited the final draft. Both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Pediatrics Perspectives
Word count: 1332
References: 9

Pulse oximetry screening (POS) is an accepted test that improves detection of critical congenital heart defects (CCHD).[1] Although outcome data are lacking, there is agreement among clinicians that POS identifies babies with CCHD before discharge. Following consideration by an expert workgroup, POS was adopted onto the US Recommended Uniform Screening Panel [2] and other countries have either introduced, or are considering introducing, POS.[1] Despite this, there is considerable variation in screening, particularly the algorithm used.[3]

Differences include: i) pre- and post-ductal saturations (right hand and either foot) versus single post-ductal measurement (foot only) and ii) timing of screening (i.e. before or after 24 hours). In algorithms using two limb measurements there are also differences - inclusion of saturations <95% in one or both limbs and the absolute value of the differential between the two in determining positive results.[1] So, which algorithm is best?

When evaluating algorithms, it is important to consider sensitivity, specificity, false positive (FP) and false negative rate. It is also vital that screening leads to timely diagnosis - before presentation with acute collapse. Meta-analysis of POS studies shows that overall, the test has modest sensitivity (~ 75%) and high specificity (99.8%), with no significant difference in sensitivity between pre/post vs. post-ductal testing or timing.[3] However, analysis of raw saturation data from babies who had both limb measurements, shows that some babies with CCHD would be missed by post-ductal testing alone.[1] In addition, the FP rate is significantly higher with earlier testing (<24 hrs).[3] These factors were deemed important by the USA workgroup considering the POS evidence and their recommendation was that screening should

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include both pre/post measurements and be performed after 24 hours.[2] This resulted in

the algorithm introduced in the USA (figure 1).[2]

A low FP rate is clearly important; but the strict definition of a FP is any test positive

baby who does not have CCHD. Interestingly, analysis of recent POS studies shows

that many FPs (30-80%) have alternative non-cardiac conditions (e.g. congenital

pneumonia, early-onset sepsis or pulmonary hypertension), which may be as equally

life-threatening as CCHD if diagnosed late.[1,4-6] These conditions may benefit from

earlier diagnosis and represent an important additional advantage. Also, important

non-critical cardiac defects (e.g. AVSD, VSD) are identified as FPs.[1,4-6] .

Timing of the test

In published studies that adopted earlier screening,[3,6] the FP rate was higher, but more

non-cardiac disease was identified; this is because such babies are more likely to

develop hypoxemia within 24 hours and therefore be picked up by earlier screening.

Careful analysis of later screening studies[4,5] reveals important additional findings. In

Granelli's[4] and Riede's[5] studies, half of eligible babies with CCHD, presented with

symptoms before screening could take place; 28/57 babies with CCHD in Granelli's

and 18/36 in Riede's. In Granelli's,[4] Over 10% of babies with CCHD (6/57) presented

with acute collapse in hospital - the very situation that screening aims to prevent. It is

well documented that babies with CCHD who collapse prior to surgery have worse

outcomes and greater risk of neuro-developmental complications,[1] so these potentially

avoidable collapses (i.e. if screening was earlier) may have significant consequences.

Although earlier screening results in more test positive babies, it is important to

balance a low FP rate with timely diagnosis. Some FP babies will be healthy- having

transitional circulation - but others have life-threatening non-cardiac conditions and

the earlier these are identified, the better. In some countries, mothers and babies are discharged from hospital within 24 hours following birth and an increasing proportion is born at home. In these circumstances, later screening in hospital is not practical. UK evidence - screening at a mean age of seven hours - reported a test positive rate of 0.8%[7] (similar to PulseOx study[6]) With around 26 000 babies screened, nine CCHDs were identified and, within the FPs, 79% had a significant medical condition. One of the major concerns regarding a high FP rate is the increased need for specialist assessment - particularly echocardiography - which can be challenging in some areas. Only 29% of test-positive babies in the UK study underwent echocardiography (mainly because an alternative non-cardiac diagnosis was established) and the echo was positive in 48%.[7] This compared favorably with babies in the same unit undergoing echocardiography for asymptomatic murmur[7]

The experience following the introduction of POS in New Jersey was recently reported.[8] Almost 73 000 babies were screened (after 24 hours) and the FP rate was 0.04%. However only three babies with CCHD and only 12 babies with non-cardiac conditions were detected. Although the FP rate is admirably low, the number of babies with CCHD is also very low. In the UK it took 2873 screens to detect one CCHD vs. 24 231 screens in the US.[7] The likelihood is, that in the US cohort, many babies with CCHD presented before screening took place. These important considerations led to the Nordic countries recommending screening at <24 hours[9]

Differences in definition of a test positive result

The UK study used the PulseOx[6] algorithm, which in addition to a difference in timing, has subtle differences in the definition of test positivity (figure 2). In the US algorithm, test positivity is defined as saturation <90% in either limb or saturations between 90-94% in *both* limbs, or a difference of >3% between the two, on 3 separate occasions (i.e. two retests each after 1 hour, before clinical assessment). In the UK, a test positive saturation must be 90-94% in *either* limb or a difference of >2% on two occasions (i.e. one retest after 2 hours which is *preceded* by clinical assessment).

Do these minor differences matter? Examining the raw pre/post saturation data from both studies and applying the US protocol to the PulseOx patients would have missed one CCHD (detected prenatally) and 2 serious CHDs. These numbers are small but may be important when scaled up nationally; further evidence is required before a precise estimate of the difference can be stated with conviction. The application of a second retest almost certainly reduces the FP rate (babies with transitional circulation improve between screens) but as the majority (up to 80%) of babies who test positive after one retest have a significant condition,[7] the second retest before clinical assessment potentially introduces a delay in diagnosis and treatment, which may result in a worse outcome.

So, should the US screening algorithm remain as it is, or should a change be considered? Countries wishing to introduce screening may, quite rightly, wish to follow tried and tested practice but unfortunately there are limited data reporting outcomes of US screening. Further research is probably unnecessary,

however collection and analysis of saturation data from populations already

being screened is required to refine the minor differences in the algorithm.

The evidence to support a change in timing is perhaps more convincing, but is

important to accept that test positives will increase (to around 0.8%) with

earlier screening and many non-cardiac conditions are identified in addition.

POS uses hypoxemia as a proxy for CCHD and does not detect CCHD directly.

Given this, should we screen for all hypoxemic conditions rather than just CCHD?

The concern is that hypoxemia is not a condition as such and newborns may

have 'physiological' hypoxemia as the cardio-respiratory systems adapt to extra-

uterine life. Once again the earlier screening takes place the more likely this

'transitional circulation' is identified in test positive babies. The other major

concern is although we have good data for CCHD, there are no robust data on the

accuracy of POS for non-cardiac conditions. This presents difficulties for Public

Health decision-makers sanctioning POS as a valid test for these conditions.

Perhaps the best compromise is to continue POS for CCHD and accept that babies

detected with non-cardiac conditions (technically FPs, but could be considered

secondary targets) are an important additional benefit. Clinical staff and parents

should be made aware of this.

Until these issues are resolved and more data forthcoming, is it worth

considering an algorithm which has a consistent slightly higher FP rate but will

potentially identify more babies with life-threatening disease?

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Measurement #1
Pulse Ox on Right Hand (RH) and One Foot After 24 Hours of Age

FAIL	RETEST	PASS
Pulse ox of 89% or less in either the RH or foot Action: Do Not Repeat for Screening, Refer for Immediate Assessment	Pulse ox of 90-94% in BOTH the RH and foot OR a difference of 4% or more between the RH and foot Action: Repeat pulse ox measurements in 1 hour	Pulse ox of 95% or more in RH or foot AND difference of 3% or less between the two Action: Do Not Repeat for Screening, Provide Normal Newborn Care

Measurement #2
Pulse Ox on Right Hand (RH) and One Foot 1 Hr After Measurement #1

FAIL	RETEST	PASS
Pulse ox of 89% or less in either the RH or foot Action: Do Not Repeat for Screening, Refer for Immediate Assessment	Pulse ox of 90-94% in BOTH the RH and foot OR a difference of 4% or more between the RH and foot Action: Repeat pulse ox measurements in 1 hour	Pulse ox of 95% or more in RH or foot AND difference of 3% or less between the two Action: Do Not Repeat for Screening, Provide Normal Newborn Care

Measurement #3
Pulse Ox on Right Hand (RH) and One Foot 1 Hr After Measurement #2

FAIL	RETEST	PASS
Pulse ox of 89% or less in either the RH or foot Action: Do Not Repeat for Screening, Refer for Immediate Assessment	Pulse ox of 90-94% in BOTH the RH and foot OR a difference of 4% or more between the RH and foot Action: Do Not Repeat, Clinical Assessment	Pulse ox of 95% or more in RH or foot AND difference of 3% or less between the two Action: Do Not Repeat for Screening, Provide Normal Newborn Care

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Figure 2 UK algorithm

Pulse oximetry (PO) before 24 hours of age or discharge measuring functional oxygen saturation in right upper and either lower limb.

SaO2<95% in either limb or >2% difference

SaO2 = 95% in both limbs and = 2% difference

Initial assessment

Abnormal

Normal

Repeat PO in 1-2 hrs

SaO2<95% in either limb or >2% difference

SaO2 = 95% in both limbs and = 2% difference

Admission to the Neonatal Unit and detailed assessment

Clinical follow-up, interrogation of cardiology database and congenital anomaly registers

CCHD Present

Other illness/CHD or Transitional circulation

CCHD Present

CCHD Absent