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Newborn Pulse Oximetry Screening: Which Algorithm is Best?

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3 **Newborn Pulse Oximetry Screening: Which Algorithm is Best?**

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

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46 defect
47

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51 be accountable for all aspects of the work.
52
53

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5 Pulse oximetry screening (POS) is an accepted test that improves detection of critical
6 congenital heart defects (CCHD).¹ Although outcome data are lacking, there is
7 agreement among clinicians that POS identifies babies with CCHD before discharge.
8
9 Following consideration by an expert workgroup, POS was adopted onto the US
10 Recommended Uniform Screening Panel ² and other countries have either introduced,
11
12 or are considering introducing, POS.¹ Despite this, there is considerable variation in
13 screening, particularly the algorithm used.³

14
15 Differences include: i) pre- and post-ductal saturations (right hand and either foot)
16 versus single post-ductal measurement (foot only) and ii) timing of screening (i.e.
17 before or after 24 hours). In algorithms using two limb measurements there are also
18 differences - inclusion of saturations <95% in one or both limbs and the absolute
19 value of the differential between the two in determining positive results.¹ So, which
20 algorithm is best?

21
22 When evaluating algorithms, it is important to consider sensitivity, specificity, false
23 positive (FP) and false negative rate. It is also vital that screening leads to timely
24 diagnosis - before presentation with acute collapse. Meta-analysis of POS studies
25 shows that overall, the test has modest sensitivity (~ 75%) and high specificity
26 (99.8%), with no significant difference in sensitivity between pre/post vs. post-ductal
27 testing or timing.³ However, analysis of raw saturation data from babies who had
28 both limb measurements, shows that some babies with CCHD would be missed by
29 post-ductal testing alone.¹ In addition, the FP rate is significantly higher with earlier
30 testing (<24 hrs).³ These factors were deemed important by the USA workgroup
31 considering the POS evidence and their recommendation was that screening should
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3 include both pre/post measurements and be performed after 24 hours.² This resulted in
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5 the algorithm introduced in the USA (figure 1).²
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8 A low FP rate is clearly important; but the strict definition of a FP is any test positive
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10 baby who does not have CCHD. Interestingly, analysis of recent POS studies shows
11
12 that many FPs (30-80%) have alternative non-cardiac conditions (e.g. congenital
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14 pneumonia, early-onset sepsis or pulmonary hypertension), which may be as equally
15
16 life-threatening as CCHD if diagnosed late.^{1,4-6} These conditions may benefit from
17
18 earlier diagnosis and represent an important additional advantage. Also, important
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20 non-critical cardiac defects (e.g. AVSD, VSD) are identified as FPs.^{1,4-6}
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25 26 Timing of the test

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28 In published studies that adopted earlier screening,^{3,6} the FP rate was higher, but more
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30 non-cardiac disease was identified; this is because such babies are more likely to
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32 develop hypoxemia within 24 hours and therefore be picked up by earlier screening.
33
34 Careful analysis of later screening studies^{4,5} reveals important additional findings. In
35
36 Granelli's⁴ and Riede's⁵ studies, half of eligible babies with CCHD, presented with
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38 symptoms before screening could take place; 28/57 babies with CCHD in Granelli's
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40 and 18/36 in Riede's. In Granelli's,⁴ Over 10% of babies with CCHD (6/57) presented
41
42 with acute collapse in hospital - the very situation that screening aims to prevent. It is
43
44 well documented that babies with CCHD who collapse prior to surgery have worse
45
46 outcomes and greater risk of neuro-developmental complications,¹ so these potentially
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48 avoidable collapses (i.e. if screening was earlier) may have significant consequences.
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51 Although earlier screening results in more test positive babies, it is important to
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53 balance a low FP rate with timely diagnosis. Some FP babies will be healthy- having
54
55 transitional circulation - but others have life-threatening non-cardiac conditions and
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3 the earlier these are identified, the better. In some countries, mothers and babies are
4 discharged from hospital within 24 hours following birth and an increasing proportion
5 is born at home. In these circumstances, later screening in hospital is not practical.
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9 UK evidence - screening at a mean age of seven hours - reported a test positive
10 rate of 0.8%⁷ (similar to PulseOx study⁶) With around 26 000 babies screened,
11 nine CCHDs were identified and, within the FPs, 79% had a significant medical
12 condition. One of the major concerns regarding a high FP rate is the increased
13 need for specialist assessment - particularly echocardiography - which can be
14 challenging in some areas. Only 29% of test-positive babies in the UK study
15 underwent echocardiography (mainly because an alternative non-cardiac
16 diagnosis was established) and the echo was positive in 48%.⁷ This compared
17 favorably with babies in the same unit undergoing echocardiography for
18 asymptomatic murmur⁷
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32 The experience following the introduction of POS in New Jersey was recently
33 reported.⁸ Almost 73 000 babies were screened (after 24 hours) and the FP rate
34 was 0.04%. However only three babies with CCHD and only 12 babies with non-
35 cardiac conditions were detected. Although the FP rate is admirably low, the
36 number of babies with CCHD is also very low. In the UK it took 2873 screens to
37 detect one CCHD vs. 24 231 screens in the US.⁷ The likelihood is, that in the US
38 cohort, many babies with CCHD presented before screening took place. These
39 important considerations led to the Nordic countries recommending screening at
40 <24 hours⁹
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3 Differences in definition of a test positive result

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5 The UK study used the PulseOx⁶ algorithm, which in addition to a difference in
6
7 timing, has subtle differences in the definition of test positivity (figure 2). In the
8
9 US algorithm, test positivity is defined as saturation <90% in either limb or
10
11 saturations between 90-94% in *both* limbs, or a difference of >3% between the
12
13 two, on 3 separate occasions (i.e. two retests each after 1 hour, before clinical
14
15 assessment). In the UK, a test positive saturation must be 90-94% in *either* limb
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17 or a difference of >2% on two occasions (i.e. one retest after 2 hours which is
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19 *preceded* by clinical assessment).
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22
23 Do these minor differences matter? Examining the raw pre/post saturation data
24
25 from both studies and applying the US protocol to the PulseOx patients would
26
27 have missed one CCHD (detected prenatally) and 2 serious CHDs. These numbers
28
29 are small but may be important when scaled up nationally; further evidence is
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31 required before a precise estimate of the difference can be stated with
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33 conviction. The application of a second retest almost certainly reduces the FP
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35 rate (babies with transitional circulation improve between screens) but as the
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37 majority (up to 80%) of babies who test positive after one retest have a
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39 significant condition,⁷ the second retest before clinical assessment potentially
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41 introduces a delay in diagnosis and treatment, which may result in a worse
42
43 outcome.
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47 So, should the US screening algorithm remain as it is, or should a change be
48
49 considered? Countries wishing to introduce screening may, quite rightly, wish to
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51 follow tried and tested practice but unfortunately there are limited data
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53 reporting outcomes of US screening. Further research is probably unnecessary,
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3 however collection and analysis of saturation data from populations already
4 being screened is required to refine the minor differences in the algorithm.
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7 The evidence to support a change in timing is perhaps more convincing, but is
8 important to accept that test positives will increase (to around 0.8%) with
9 earlier screening and many non-cardiac conditions are identified in addition.
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11 POS uses hypoxemia as a proxy for CCHD and does not detect CCHD directly.
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15 Given this, should we screen for all hypoxemic conditions rather than just CCHD?
16

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18 The concern is that hypoxemia is not a condition as such and newborns may
19 have 'physiological' hypoxemia as the cardio-respiratory systems adapt to extra-
20 uterine life. Once again the earlier screening takes place the more likely this
21 'transitional circulation' is identified in test positive babies. The other major
22 concern is although we have good data for CCHD, there are no robust data on the
23 accuracy of POS for non-cardiac conditions. This presents difficulties for Public
24 Health decision-makers sanctioning POS as a valid test for these conditions.
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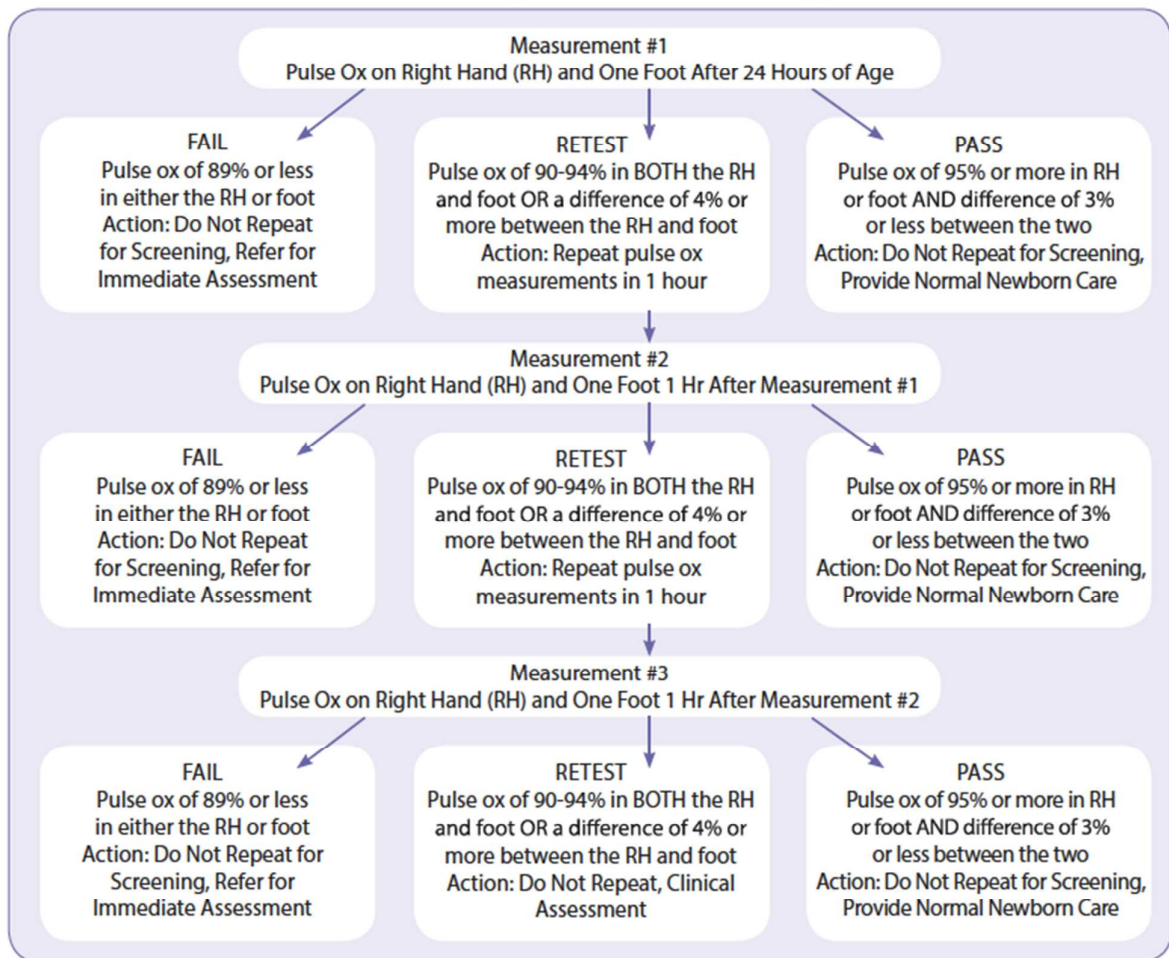
27
28 Perhaps the best compromise is to continue POS for CCHD and accept that babies
29 detected with non-cardiac conditions (technically FPs, but could be considered
30 secondary targets) are an important additional benefit. Clinical staff and parents
31 should be made aware of this.
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46 Until these issues are resolved and more data forthcoming, is it worth
47 considering an algorithm which has a consistent slightly higher FP rate but will
48 potentially identify more babies with life-threatening disease?
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Figure 1. USA algorithm



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Figure 2 UK algorithm

