

## ORIGINAL ARTICLE

Clinical practices in neonatal oxygenation: where have we failed?  
What can we do?A Sola<sup>1</sup>, YP Saldeño<sup>1,2</sup>, V Favareto<sup>1,3</sup><sup>1</sup>Mid Atlantic Neonatology Associates and Atlantic Neonatal Research Institute, Atlantic Health System, Morristown, NJ, USA; <sup>2</sup>Complejo Hospitalario de Ourense, Ourense, España and <sup>3</sup>Hospital Provincial de Rosario, Rosario, Santa Fe, Argentina

**Introduction:** Oxygen is among the most frequently used therapies in neonates worldwide. Nevertheless, many times it is used unnecessarily. Neonatal practices have changed over the last several years; treatments originally believed to be beneficial have been discarded.

**Study Design:** Oxygen utilized 'just in case' or 'prophylactically' can lead to great damage previously ignored and/or unseen by healthcare providers.

**Conclusion:** It is imperative to improve education on neonatal oxygenation and saturation monitoring. It is also important not to depend on old assumptions, which were not based on evidences. The potential for unseen damage at the cellular and tissue levels cannot be ignored. Therapies that prove to be outdated or even dangerous must be eliminated while further research and confirmation of the best practices are determined. Freedom to choose can come at a price.

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**Keywords:** pulse oximetry; oxygen; oxygen saturation; oxygenation; neonatal clinical practices; outcome improvement

## Introduction

Oxygen is the most common drug used in neonatology worldwide. Based on the important and necessary objective of preventing hypoxia, many newborn infants are exposed to high levels of oxygen. There are many pathophysiological conditions that may lead to tissue hypoxia, but the cause of hyperoxemia is the healthcare itself. Unnecessary, even brief, neonatal exposures to oxygen when not indicated must be limited, if not avoided. Furthermore, readings >95% in oxygen saturation monitors (SpO<sub>2</sub>) are potentially dangerous in infants who are breathing the oxygen. Practice changes need to be made. These practice changes requires a multidisciplinary effort, a different attitude and continued assessment. The future of many babies is related to how oxygen is administered.

The optimal oxygen dose in all cases is not always known, but some previous errors and incorrect practices need to be abandoned.

Karl Popper said, 'Science is the ability to discover errors, not the truth.' The objective of this paper is to provide a summary on neonatal oxygen toxicity and propose different practice approaches aiming to avoid potential adverse effects of hyperoxia and improve unnecessarily high rates of neonatal morbidity outcomes.

## What do we know?

Claude Bernard wrote, 'It is the things we do know that are the great hindrance to our learning of the things we do not.'<sup>1</sup> In a survey of more than 4300 responders, about 70% of the care providers recognized they do not have a complete education in neonatal oxygenation,<sup>2</sup> and have insufficient knowledge of the alveolar gas equation and other basic concepts. Furthermore, 92% did not know how SpO<sub>2</sub> monitors work and the differences between different SpO<sub>2</sub> monitors.<sup>2</sup>

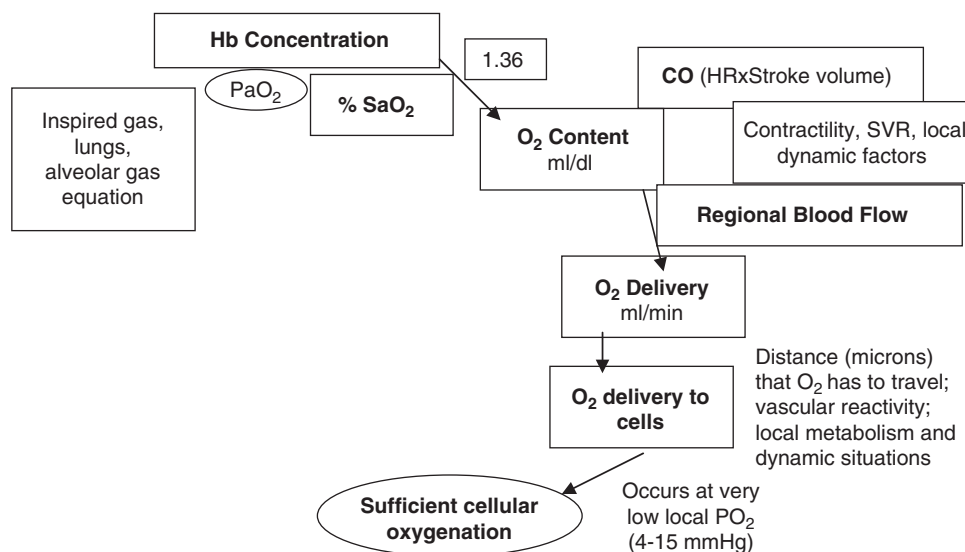
Julius Comroe Jr wrote in the preface of his book of 1955, 'Pulmonary physiologists understand pulmonary physiology reasonably well. Many doctors and medical students do not.'<sup>1,3</sup> It would seem, therefore, that educators have failed, both then and now, in providing adequate education to bedside care providers.

The lag in making necessary improvements in oxygen practices can be due in part to insufficient education, delays in accepting the hazards of excessive oxygen and existing guidelines promulgated handed down by authoritative bodies. On this subject, Francis Bacon said, 'Authority criterion is without value. The idea that something is true because it was said by wise men is a bad principle.' And Claude Bernard adds, 'When we meet a fact which contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names and generally accepted.'

The story of neonatal oxygenation continues because, as is almost always true in science, many issues still require further understanding and many questions still need answers.

## Oxygenation and hyperoxygenation

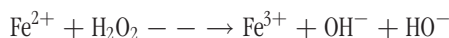
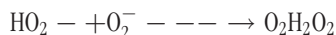
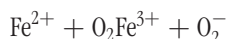
Adequate cellular oxygenation depends on many factors (Figure 1); one of the least important is the PaO<sub>2</sub>. About 2% of the oxygen consumed by humans produces reactive oxygen species (ROS).<sup>4</sup>



**Figure 1** Summary of factors involved in leading to sufficient cellular oxygenation. H, hemoglobin; SaO<sub>2</sub>, arterial oxygen saturation; CO, cardiac output; SVR, systemic vascular resistance. 1.36 is a constant.

If the production of hydroxyl radical and peroxynitrite exceeds the catabolism, oxidative damage to DNA appears, leading to a variety of diseases.

The oxidation is dependent upon NAD(P)H, O<sub>2</sub> and Fe<sup>3+</sup> or Cu<sup>2+</sup>. After oxidative modification, proteins become highly sensitive to proteolytic degradation and, in the case of enzymes, they convert to catalytically inactive or less active thermo labile forms.<sup>5</sup> Iron is the transitional metal with the highest concentration of all such metals in living organisms and is thought to be responsible for most of the abnormal ROS production observed. Iron can generate ROS and hydroxyl radicals by several mechanisms; one is shown below.



When we give infants oxygen we are giving a drug and, as Comroe said, 'No drug produces only the effect for which it is prescribed. It invariably affects other functions and organ systems.'<sup>1,3</sup> In addition to being a drug, excessive oxygen meets the necessary criteria to be considered a health hazard.<sup>6</sup>

### Current neonatal monitoring of oxygen administration and physiology

Better methods than PaO<sub>2</sub> and SpO<sub>2</sub> for assessing tissue oxygenation and altered redox status in clinical practice may some day become available. Until then, identifying practices that reduce the risk of potential hyperoxic damage can only be beneficial for many babies.

### Arterial oxygen saturation

SpO<sub>2</sub> is considered the fifth vital sign,<sup>6</sup> of value to detect hypoxemia, but it cannot reveal hyperoxemia. SpO<sub>2</sub> monitors were introduced into practice without adequate education for healthcare providers responsible for data interpretation and administration of the fraction of inspired oxygen (FiO<sub>2</sub>). Therefore, the monitors are not well understood by many clinicians. In addition, the performance of SpO<sub>2</sub> monitors is not uniform. The advantages of SpO<sub>2</sub> monitors with signal extraction technology (Masimo SET) during situations of low perfusion and motion have been previously described.<sup>7-11</sup>

SpO<sub>2</sub> monitoring is based on the relation between hemoglobin (Hb) and oxygen. Bohr showed that the dissociation curve was sigmoid shaped, with an initial relative horizontal portion, followed by a vertical one, ending again with a horizontal shape. When PaO<sub>2</sub> is low, Hb gets rid of the oxygen, so the little oxygen available is given to the tissues. On the other hand, Hb affinity for oxygen increases as successive molecules of oxygen bind after a certain PaO<sub>2</sub> level has been reached.<sup>12</sup> At such point, and as PaO<sub>2</sub> increases, more molecules bind to Hb, until the maximum amount is reached (100% saturation).

The fetus grows without difficulty *in utero* with blood that is about 70 to 75% saturated.<sup>13</sup> Many things must change for a successful transition from fetal to neonatal life. One of them is the progressive increase in arterial oxygen saturation (SaO<sub>2</sub>) until the normal neonatal SaO<sub>2</sub> in room air (95 to 100%) is reached. This may take several minutes after birth, and, therefore, we should not aim for a saturation >90% immediately after birth.<sup>14,15</sup> The neonatal PaO<sub>2</sub> is around 55 to 75 mm Hg, rarely >80 mm Hg, based on the alveolar gas equation and intra- and extrapulmonary shunts. However, when we give infants FiO<sub>2</sub>>0.21, it is impossible to predict how high the PaO<sub>2</sub> is when the SaO<sub>2</sub> is 97 to 100%.

Factors that affect the SaO<sub>2</sub> of Hb are shifts in the O<sub>2</sub>–Hb dissociation curve depending on 2 to 3 DPG content, HbF concentration and Bohr's effect. They all affect the P<sub>50</sub>.<sup>6</sup> P<sub>50</sub> is the O<sub>2</sub> tension (PaO<sub>2</sub> in mm Hg) when the binding sites of Hb are 50% saturated. The P<sub>50</sub> is inversely related to the binding affinity of Hb for oxygen, that is, the higher the affinity, the sooner the Hb will be 50% saturated; the P<sub>50</sub> will be lower and the curve shifted to the left. SaO<sub>2</sub> and Hb concentration determine the blood oxygen content (ml of O<sub>2</sub> per 100 ml of blood). Oxygen delivery to the tissues and cells depends on this and is influenced by O<sub>2</sub> consumption and the complex interplay of many factors (Figure 1).

### Tension of arterial oxygen (PaO<sub>2</sub>)

We do not know which value of PaO<sub>2</sub> is critical in neonates. All neonatal clinicians surveyed would not allow a PaO<sub>2</sub> <40 mm Hg for too long, but varying percentages would accept PaO<sub>2</sub> 40 to 45 mm Hg and more will tolerate PaO<sub>2</sub> 45 to 50 mm Hg, without further increasing FiO<sub>2</sub>, if the infant is otherwise well. A PaO<sub>2</sub> of 40 mm Hg may saturate Hb 85%. If the Hb concentration were 14 g dl<sup>-1</sup>, oxygen content would be about 17 ml dl<sup>-1</sup> (14 × 1.36 × SaO<sub>2</sub>, Figure 1). This oxygen content is likely to be sufficient to avoid neonatal tissue hypoxia at usual ranges and interactions of the factors described in Figure 1 with oxygen consumption. On the other extreme, a PaO<sub>2</sub> >80 mm Hg may be too high for newborns. Above a certain, though not precisely known, PaO<sub>2</sub> level, the dissolved PaO<sub>2</sub> is unnecessary and potentially harmful. How frequent the is risk for injury and oxidant damage with PaO<sub>2</sub> >80 mm Hg is unknown, as it is with PaO<sub>2</sub> >70 mm Hg, >75 mm Hg or >90 mm Hg. However, why expose infants to risk (as low as it may be) if lower PaO<sub>2</sub> without hypoxemia can meet all demands at the tissue and cellular levels?

The relation between SpO<sub>2</sub> readings and the 'gold standard' SaO<sub>2</sub> by co-oximeter is also complex. A saturation value measured by a blood gas machine should never be used. The Food and Drug Administration requires that SpO<sub>2</sub> monitors be calibrated to display functional saturation. However, the bias, accuracy and precision of the equipment are different, more so during unstable conditions and at lower SpO<sub>2</sub>. Differences >3% between SpO<sub>2</sub> readings and the true SaO<sub>2</sub> may exist. Since some monitors are better than others, a similar or even larger disparity in SpO<sub>2</sub> simultaneous readings between different SpO<sub>2</sub> monitors exists.<sup>7–11,16</sup> When SpO<sub>2</sub> is 97% in one monitor, the true SaO<sub>2</sub> and the SpO<sub>2</sub> in another monitor could be 100%. Therefore, accepting the imprecision of the real world, the one SpO<sub>2</sub> value cannot be the sole focus. It is much more reasonable to work with ranges of SpO<sub>2</sub>.

### SpO<sub>2</sub> and PaO<sub>2</sub>

How high is the PaO<sub>2</sub> in infants breathing FiO<sub>2</sub> >0.21 when SpO<sub>2</sub> reads 100%? It is impossible to know the exact answer, since

**Table 1** Incidence of PaO<sub>2</sub> >80 mm Hg and PaO<sub>2</sub> <40 mm Hg according to FiO<sub>2</sub> and SpO<sub>2</sub> range in 976 samples in seven NICUs

	SpO <sub>2</sub> >94%	SpO <sub>2</sub> 85–93%
<i>PaO<sub>2</sub> &gt;80 mm Hg</i>		
FiO <sub>2</sub> >0.21	60%	4%
FiO <sub>2</sub> 0.21	16%	0%
<i>PaO<sub>2</sub> &lt;40 mm Hg</i>		
FiO <sub>2</sub> >0.21	0.5%	8%
FiO <sub>2</sub> 0.21	0%	1%

% represents the percent of samples for each specific SpO<sub>2</sub> range and FiO<sub>2</sub> category that had PaO<sub>2</sub> >80 mm Hg or PaO<sub>2</sub> <40 mm Hg.<sup>17</sup>

the SpO<sub>2</sub>/PaO<sub>2</sub> relationship is flat in the upper part of Hb–O<sub>2</sub> dissociation curve. The neonatal PaO<sub>2</sub> in a case like this could be 65 to 75 mm Hg, >90 mm Hg or >350 mm Hg. A better question would be: What is the risk of PaO<sub>2</sub> >80 mm Hg in infants breathing supplemental oxygen when SpO<sub>2</sub> reads 95 to 100%? And, what is the *risk* of PaO<sub>2</sub> <40 mm Hg when a baby is breathing FiO<sub>2</sub> to maintain SpO<sub>2</sub> 85 to 93%? Table 1 summarizes this paper's findings.<sup>17</sup> PaO<sub>2</sub> <40 mm Hg occurred very infrequently and mostly with SpO<sub>2</sub> 85 to 90%. This PaO<sub>2</sub> may be too low for a specific infant. As in practice, the PaO<sub>2</sub> was repeated and it was either found to be >40 mm Hg or the infant's PaO<sub>2</sub> improved following a minimal FiO<sub>2</sub> increase.<sup>17</sup>

The risk of PaO<sub>2</sub> >80 mm Hg in infants breathing FiO<sub>2</sub> >0.21 who had SpO<sub>2</sub> 95 to 100% was high (Table 1). PaO<sub>2</sub> >80 mm Hg occurred much less in newborns in room air. This can be explained by adequate pulmonary blood flow, minimal extra- and intrapulmonary shunting (as it can occur with CPAP or IMV), lower alveolar pressures of CO<sub>2</sub> and subsequent increase in alveolar pressure of oxygen. Whether PaO<sub>2</sub> >80 mm Hg is always associated with more oxidant damage and, if so, to what degree, remains to be fully investigated.

### Improving morbidity when changing clinical practice of oxygen delivery and monitoring

Today's best neonatal clinical practice has led to improved outcomes,<sup>18</sup> but many neonatal practices may be impacting the neonatal brain unfavorably.<sup>19,20</sup> Excess oxidative stress is likely to be caused only by our clinical actions or inactions, including iron administration,<sup>20–23</sup> phototherapy<sup>24</sup> and oxygen. We must turn off the lights and the oxygen when not necessary to avoid a potentially bad combination.<sup>24</sup>

Oxygen, a potent oxidant, is a health hazard if inhaled in excess.<sup>9</sup> Healthcare providers are the ones who choose to administer oxygen for babies to inhale. The potential detrimental effects associated with oxygen include retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), increase length of

**Table 2** Trying to avoid hyperoxemia in the delivery room, NICU, transport, operating room and during diagnostic studies

1. Care to prevent hyperoxemia must commence in the delivery room
2. Administer supplemental oxygen only when really needed
3. Be able to mix gases (air and oxygen) and know the dose (concentration; i.e., FiO<sub>2</sub>) of supplemental oxygen the infant is receiving
4. Measure FiO<sub>2</sub> each and every time oxygen is given to newborns
5. Be able to measure levels of blood oxygenation as best as possible. Today this can be done with accurate and state of the art pulse oximetry monitors (SpO<sub>2</sub> monitors)
6. Never use pure oxygen (100%, FiO<sub>2</sub> 1.0) unless it is really proven to be necessary
7. Do not use nitrogen washout (FiO<sub>2</sub> 1.0) for a pneumothorax. No important outcome was ever shown to improve with this practice, and PaO<sub>2</sub> can be very high (i.e., >150 mm Hg) for a long time
8. Never leave a preterm infant for any period of time breathing supplemental oxygen, just because the infant breathes a little fast or has some grunting or looks pinker being nursed in oxygen. (Always document that you indeed need to give supplemental oxygen by a reading of abnormally low SpO<sub>2</sub>)
9. SpO<sub>2</sub> monitors were developed for detection of hypoxemia and are of no value for detecting hyperoxemia
10. Do not allow the SpO<sub>2</sub> monitor to read >94–95% when a preterm infant is breathing supplemental oxygen
11. Do not permit hypoxemia
12. Manual ventilation: should never be done with gas flowing into a breathing bag directly from the wall oxygen flow meter (i.e., 100% or FiO<sub>2</sub> 1.0). The gas from the wall is pure oxygen and is *cold* and *dry*
13. Use of an accurate SpO<sub>2</sub> monitor with preset low and high alarms, which must never be left turned off
14. Aim for a target SpO<sub>2</sub> range which is wide enough so that there are fewer possibilities of frequent changes and of chasing SpO<sub>2</sub> values
15. Do not aim for normal SpO<sub>2</sub> values (i.e., >95%) in preterm infants breathing supplemental oxygen. These are high SpO<sub>2</sub> levels, which are unnecessary and very likely detrimental
16. When a premature infant is breathing O<sub>2</sub>, and the SpO<sub>2</sub> is 96–100%, the PaO<sub>2</sub> can be >90 mm Hg
17. Always wean the FiO<sub>2</sub> (slowly) when SpO<sub>2</sub> is >95% in a preterm infant breathing supplemental oxygen. If saturation remains at >95% in room air (FiO<sub>2</sub> 0.21), this is an indication the infant did not need supplemental oxygen

stay (LOS), impaired brain development and possibly infection and cancer.

ROP remains the leading cause of blindness and vision impairment in children, despite advances in care.<sup>18,25–29</sup> Low birth weight and gestational age are the single most important predictors for the development and severity of ROP, correlating with the area of avascular retina at birth.<sup>30–34</sup> The pathogenesis of ROP is complex and biphasic, involving growth factors and abnormal retinal vascular migration with an early vaso-obliterative phase followed by a proliferative, vascular phase.<sup>35</sup> High PaO<sub>2</sub> and repeated fluctuating cycles of hyperoxia and hypoxia favor the progression of ROP in animals and humans.<sup>36–38</sup> In 2003, we reported the results of changing clinical practice following an

educational program provided to all neonatal intensive care unit (NICU) staff<sup>39</sup> to implement and enforce clinical practices of oxygen management and monitoring. Tight SpO<sub>2</sub> control with modern monitoring (Masimo SET) markedly reduced the development of stages 3 and 4 ROP and the need for laser therapy in infants 500 to 1500 g.<sup>39</sup> Recently, we reported improvement in ROP rates when avoiding hyperoxia in infants <1250 g at two different centers and investigated if the effect of this practice was associated with worsening short term outcomes and long term neurodevelopment.<sup>40</sup> At the time of these prospective studies, there were surveys or cohort studies that also supported an association with less ROP in different centers utilizing different SpO<sub>2</sub> targets.<sup>41–43</sup> Recently, several studies<sup>44–46</sup> have confirmed our findings. Wright *et al.*<sup>44</sup> concluded that SPO<sub>2</sub> between 83 and 93% and avoiding oxygen fluctuations prevent the early vaso-obliterative phase and subsequent severe ROP. We found only one study suggesting that changing practice is not associated with improvements in ROP.<sup>47</sup>

There are other potential benefits of avoiding high SpO<sub>2</sub> targets and decreasing the amount of oxygen given to infants. We have recently shown that changing SpO<sub>2</sub> saturation targets, to try to avoid hyperoxia, resulted in a decrease in BPD from 51 to 35% ( $P < 0.001$ ) in infants <1250 g who received IMV and oxygen therapy.<sup>18,40</sup> The practice was also associated with decreased LOS from  $85.9 \pm 40$  to  $76.5 \pm 37.7$  days ( $P = 0.01$ ).<sup>40</sup> This change in practice was not associated with worse survival or morbidity rates of PDA, NEC, IVH or PVL. This change in practice, did not have a detrimental effect on neurodevelopmental outcomes at 18 months corrected age, but the Bayley scores actually improved.<sup>40</sup> From these large studies we estimated that with lower SPO<sub>2</sub> limits, six cases of BPD and 12 cases of ROP are prevented for every 100 infants <1250 g treated.

Sepsis is one of the leading causes of morbidity and mortality in the neonatal unit. Oxygen is an immune modulator. If the antioxidant mechanism is deficient or overwhelmed by excess oxygen, the harmful and toxic effects of ROS could depress the immune response. Our preliminary study suggests that aiming to avoid hyperoxia in neonatal practice may have a significant association in the reduction of late bacterial sepsis, from 48 to 28% ( $P < 0.001$ ).<sup>48</sup>

We recently reported that the response to this change in practice yields better effects in girls than in boys.<sup>49</sup> This finding lends support to the different treatment-by-gender effect reported in other areas and to the fact that we do not know which is the optimal saturation value for all babies at all times.

Mental changes with oxygen therapy in human adults were reported by Comroe over 50 years ago.<sup>3</sup> The developing brain is particularly susceptible to oxygen as confirmed by basic investigations. This seems to be the case in human neonates. Hyperoxia independently contributed to the risk of disabling cerebral palsy (CP) in very-low birth weight infants mechanically

ventilated<sup>50</sup> and was also found to increase adverse outcomes, including CP, after perinatal hypoxia-ischemia encephalopathy in term newborns.<sup>51</sup> The better long-term neurodevelopmental scores in preterm infants managed with practices to prevent hyperoxia<sup>40</sup> concur with these findings. Additionally, a study with functional MRI described that 14 healthy children exposed to two minutes of 100% oxygen showed alterations in the insula, hypothalamus and hippocampus,<sup>52</sup> supporting that 100% oxygen unleashes a cascade of harmful chemicals that can influence central nervous function very quickly.

The risk of high PaO<sub>2</sub> may start during the first minutes of life. In the delivery room, oxygen may trigger a cascade of events that may be impossible to stop, despite the best NICU care.<sup>53</sup> Newborns are not supposed to be pink in the first several minutes. Pure oxygen must be avoided because of its toxicity even for a short period of time.<sup>54–56</sup> Saugstad and Vento<sup>53–55</sup> demonstrated that 100% oxygen is much worse than room air resuscitation in terms of mortality, which was clearly confirmed by a recent meta-analysis.<sup>57</sup> Furthermore, the oxidative stress of pure oxygen lasts at least for 4 weeks after birth,<sup>58</sup> and there could be more myocardial and kidney injury. Animal studies have also shown that 100% oxygen activates transcription factors, leads to thrombocyte aggregation,<sup>59</sup> increases oxidative stress, neurologic and brain damage,<sup>60,61</sup> inflammation in the lung and heart and may also trigger pulmonary hypertension.<sup>62</sup>

Finally, who would have imagined that only a few minutes of oxygen could be associated with childhood cancer? A small fraction of the oxygen consumed by the mitochondria is constantly

converted to superoxide radical anions, hydrogen peroxide, hydroxyl radicals and other ROS. Their excess can modify the intracellular redox status, altering signal transduction, enzyme activation and protein, DNA and RNA synthesis, leading to aging and cancer.<sup>63</sup> Two independent investigators<sup>64,65</sup> described that the exposure to 100% oxygen at birth is associated with childhood leukemia and cancer, showing that nearly 15% of cancers might be prevented if oxygen had been avoided. It was estimated that 17 to 18 per 10 000 children exposed to oxygen for more than 3 min in the delivery room might develop cancer, compared to six unexposed infants.<sup>66</sup> Some people may disregard these as small numbers, but neonates do not choose what they breathe. Healthcare providers do that for them.

### Clinical practices

It is clear that changes in practices are necessary, trying to avoid neonatal hyperoxemia in the delivery room, the NICU, the operating room and during transport and diagnostic studies. We summarize some of these practices in Table 2.

In Table 3 we summarize some other issues regarding clinical care with supplemental oxygen, in order to improve neonatal daily care of oxygen administration and monitoring. These issues include necessary equipment, clinical assessment and actions during procedures, apnea and manual ventilation. In addition, Table 3 presents one approach regarding increases and wide fluctuations of FiO<sub>2</sub> and stresses the important issues of not turning SpO<sub>2</sub> alarms off and keeping SpO<sub>2</sub> readings within acceptable SpO<sub>2</sub>

**Table 3** Clinical care of newborns to whom we give supplemental oxygen

<i>Issue</i>	<i>Actions</i>	<i>Other factors to consider</i>
Equipment	Blender and state of the art SpO <sub>2</sub> monitor	Measure dose (FiO <sub>2</sub> ) and levels (SpO <sub>2</sub> ) at all times, also in DR
Think twice	Ask yourself: Does this baby really need this FiO <sub>2</sub> ?	Think again
Assess again	Do not give O <sub>2</sub> unless a clear need is demonstrated	Prematurity, tachypnea, grunting, acrocyanosis, apnea and others are not an indication
Delivery room	Do not blow by O <sub>2</sub> Do not use 100% O <sub>2</sub> unless its need is really proven	Remember the transition from fetal to normal neonatal saturation
For procedures (i.e., suction of airway)	Do not increase FiO <sub>2</sub> before starting	If problems, remember PEEP to maintain FRC
Require episodes of manual ventilation	Do not increase previous FiO <sub>2</sub> routinely	This is very important
Apnea with need for manual ventilation	Ventilate! (Do not increase previous FiO <sub>2</sub> routinely)	If it was really necessary to increase FiO <sub>2</sub> , watch SpO <sub>2</sub> readings and return FiO <sub>2</sub> to baseline rapidly
If FiO <sub>2</sub> needs to be increased	Document in records. Do not leave bedside. Assess and re-assess. See SpO <sub>2</sub> readings and alarms. Do not allow SpO <sub>2</sub> reading to remain >94–95% <sup>a</sup>	Assess if FiO <sub>2</sub> can be brought to previous level, in a stepwise manner as long as SpO <sub>2</sub> is stable and >93–94%.
Avoid wide fluctuations of FiO <sub>2</sub>	May lead to see-saw of SpO <sub>2</sub>	Alternating between hypoxia and hyperoxia is risky to the eyes
SpO <sub>2</sub> alarm setting	(83%) 85–93% (94%)	No need to argue for an exact value
Alarms	Operative all of the time	A must
SpO <sub>2</sub> readings	Do not 'chase them'	Evaluate infant and monitor before modifying FiO <sub>2</sub>
SpO <sub>2</sub> readings	If SpO <sub>2</sub> is as good as normal in room air: Act!	Do not allow SpO <sub>2</sub> reading to remain >94–95% <sup>a</sup>

<sup>a</sup>Exceptions are the rules of life. A few infants breathing supplemental oxygen may need SpO<sub>2</sub> >95% some time, infrequently though.

ranges. Finally, it is imperative to decrease the  $\text{FiO}_2$  if the  $\text{SpO}_2$  reading is as good as it is normally in room air (Table 3).

## Conclusion

In the newborn, oxygen is more toxic than originally believed. Our understanding of the potential serious toxic damage that we can induce by administering excessive oxygen to breathe is improving.

We have failed in clinical practice by exposing many newborns worldwide to high oxygen levels and hyperoxic states when trying to prevent hypoxia. What can we do? Remind ourselves that treating hypoxemia is not the same as inducing hyperoxia. We must move forward with the objective of not permitting hypoxemia. At the same time, we must make every effort to avoid hyperoxia (Tables 2 and 3). We cannot forget that in clinical care we cannot see many important factors at the cellular and tissue level. Only healthcare providers can induce hyperoxia and its inherent risks. A future goal in clinical care would be to find better  $\text{SpO}_2$  limits or different technologies that can assist clinicians in eliminating hyperoxemia and hypoxemia during the neonatal period. Until this happens, we should change general practice, aiming to avoid hyperoxia without permitting hypoxemia.

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