THE DELICATE BALANCE:
MANAGING OXYGEN TREATMENT IN NEONATES

This review is based on a presentation given at the National Association of Neonatal Nurses (NANN) 33rd Annual Education Conference Providence, Rhode Island, on October 11, 2017

Mallinckrodt Pharmaceuticals

This article was supported and sponsored by Mallinckrodt Pharmaceuticals

The Delicate Balance:
Managing Oxygen Treatment in Neonates

This review is based on a Mallinckrodt Pharmaceuticals-sponsored presentation, "The Delicate Balance of Managing Oxygen Treatment in Neonates," delivered by Amy R. Koehn, PhD, NNP-BC, at the National Association of Neonatal Nurses (NANN) 33rd Annual Conference, held in Providence, Rhode Island on October 11, 2017. In addition to focusing on the potential risks associated with exposing newborn tissues to episodes of lower (hypoxic) and higher (hyperoxic) than normal concentrations of serum oxygen, the current guidance for target saturation ranges and methods of tissue oxygenation measurements in neonates was reviewed. A total of 181 neonatal nurses, neonatal nurse practitioners, nurse educators, and nurse managers were polled during the presentation using an audience response system (ARS). Results from this poll and two similar polls from previous years are discussed.

Financial Support and Sponsorship: This article was written by MedEdNow, LLC, through the support and sponsorship of Mallinckrodt Pharmaceuticals. Dr. Amy R. Koehn is a paid consultant of Mallinckrodt Pharmaceuticals.

"We've had the pendulum swing in both directions. Now we're trying to find where that middle ground is."

–Amy R. Koehn, PhD, NNP-BC

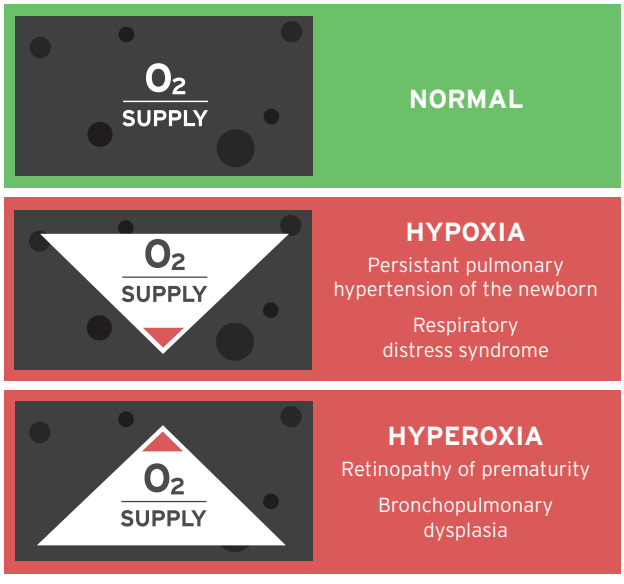


Figure 1. The figures above outline diseases associated with exposure to hypoxia and hyperoxia.[1-7] The figures labeled "O_2 Supply" refer to the supply of oxygen in the blood and tissue.

Oxygen is essential for biological processes, especially in developing newborns.[8,9] They experience respiratory distress when oxygen intake is insufficient to meet the demands of the growing body. The resultant hypoxemia, or low concentrations of oxygen in the blood, can damage tissues and even lead to death if left untreated **(Figure 1)**.[10, 11] Supplemental oxygen is used to treat this condition and when managed correctly, can help improve tissue oxygenation.[8,9] However, accumulating evidence suggests that high concentrations of supplemental oxygen can damage tissue and organs and that current management strategies may not address both the supply and the demand sides of oxygenation **(Figure 1)**.[1-5] Moreover, the levels of oxygenation within a population vary across a continuum. Therefore, creating a generalized approach for optimizing oxygenation in each patient may be difficult to achieve.[12,13]

Oxygen use in neonatal intensive care continues to evolve in conjunction with our understanding of the risks associated with oxygen exposure. Bonnaire was the first to report that a lack of oxygen contributed to hypoxia, or as he described it: a "blue baby."[14] Early reports by Rotch and others in the 1890s described the administration of oxygen as a key component to managing preterm neonates.[15] With oxygen use becoming increasingly common, oxygen delivery soon became an indispensable part of treating hypoxia in this and other patient populations.[16,17] By the late 1960s and early 1970s, clinicians began describing lung damage in neonates as associated with the use of high concentrations of oxygen and positive pressure ventilation.[17-19] Since then, an increasing number of clinicians have urged their colleagues to avoid hyperoxemia and to use oxygen judiciously when treating hypoxemia.[18] Now, a patient's serum oxygen levels are regularly assessed to guide oxygen supplementation and manage tissue oxygenation. Yet this approach does not consider

whether a measured serum oxygen level is sufficient for the demand of the patient's tissues **(Figure 2)**.[12,13] This could be described as the oxygen saturation conundrum.

The Oxygen Saturation Conundrum

Peripheral capillary oxygen saturation (SpO_2) is a measurement of the percentage of oxygen-bound hemoglobin.[20] While an SpO_2 measurement can be helpful in assessing oxygen levels in the blood, it does not reveal whether the oxygen demand of the tissue is being met. Certain pathological conditions and neonatal treatments can influence oxygen demand in tissue. Pathological conditions, such as sepsis, fever, and infections have been found to elevate oxygen demand.[21,22] In addition, oxygen demand can increase with motor activity (in the form of agitation, shivering, seizures) and with increased work of breathing.[21,23] In contrast, the use of sedation and neuromuscular blockers can decrease muscular activity, decrease agitation, and inhibit catecholamine production thereby decreasing the consumption of oxygen.[21,23] Clinical use of hypothermia also reduces the oxygen demands of the body.[24]

There are numerous variables that influence the demand of oxygen in tissues, and therefore the consequences of using or not using supplemental oxygen can vary widely from patient to patient and from moment to moment. The consensus view is that dissolved oxygen in serum causes hyperoxia in tissue.[25,26] The use of supplemental oxygen in a patient with a high oxygen saturation measurement and low oxygen demand can increase the levels of dissolved oxygen in the blood and the risk of complications associated with hyperoxia. However, a high oxygen saturation measurement in a patient on supplemental oxygen can have less risk for hyperoxia if the oxygen demand is high. Similarly, a low oxygen saturation measurement can have less risk of complications associated with hypoxia in a patient with a low oxygen demand, but there will be a high risk if the oxygen demand is high **(Figure 2)**. Day-to-day and even moment-to-moment variations in a patient's oxygen demand make it difficult for clinicians to determine what oxygen saturation levels are safe and appropriate at a given time and in a specific circumstance.[13]

The Role of Oxygen Exposure in the Formation of Energy and Reactive Oxygen Species

Oxygen demand stems from the use of oxygen in cells to produce energy in the form of adenosine triphosphate (ATP). Energy production begins when pyruvate, the

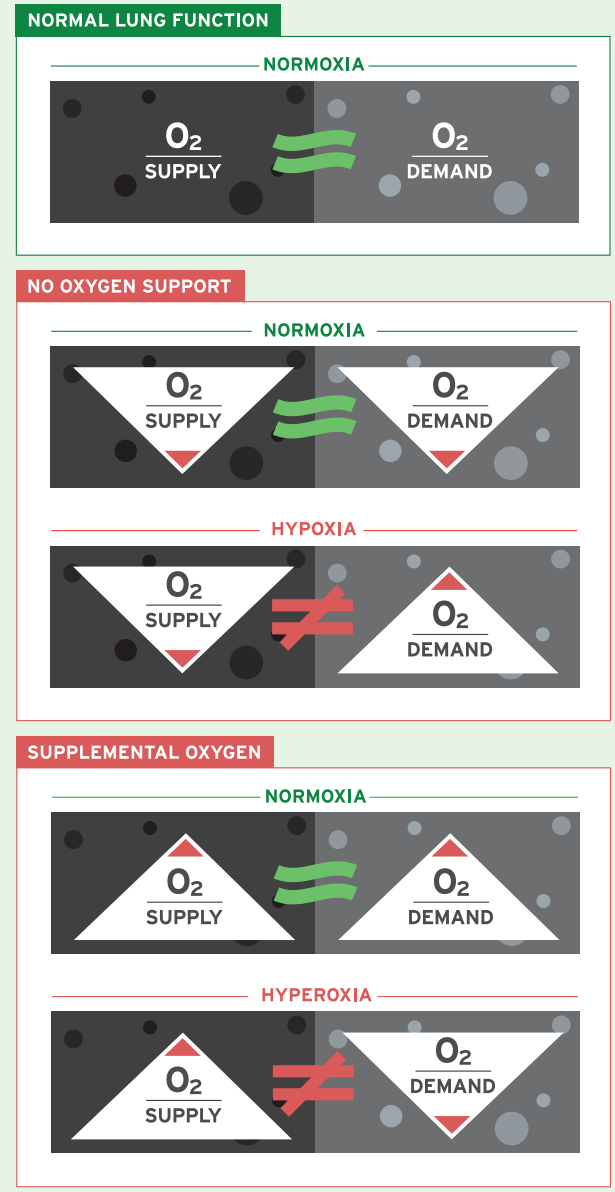


Figure 2. The figure above represents the relationship between oxygen delivery and oxygen demand. In the figure, "O_2 Supply" refers to the supply of oxygen in the blood and tissue, and "O_2 Demand" refers to the demand for oxygen in tissues. A) Oxygen delivery often meets oxygen demand in patients with normal lungs. B) Normoxia can sometimes be achieved in patients with lung disease when low levels of oxygen are sufficient to meet a low demand for oxygen. Hypoxia results when these low levels of oxygen are insufficient for the demands of the tissue. Normoxia can also be achieved in patients with lung disease using supplemental oxygen. Supplemental oxygen can produce a normoxic state if delivered oxygen is sufficient for the level of oxygen demand in the tissues. Hyperoxia can occur with supplemental oxygen when the tissue oxygen demand is lower than the quantities of oxygen entering the bloodstream.[13]

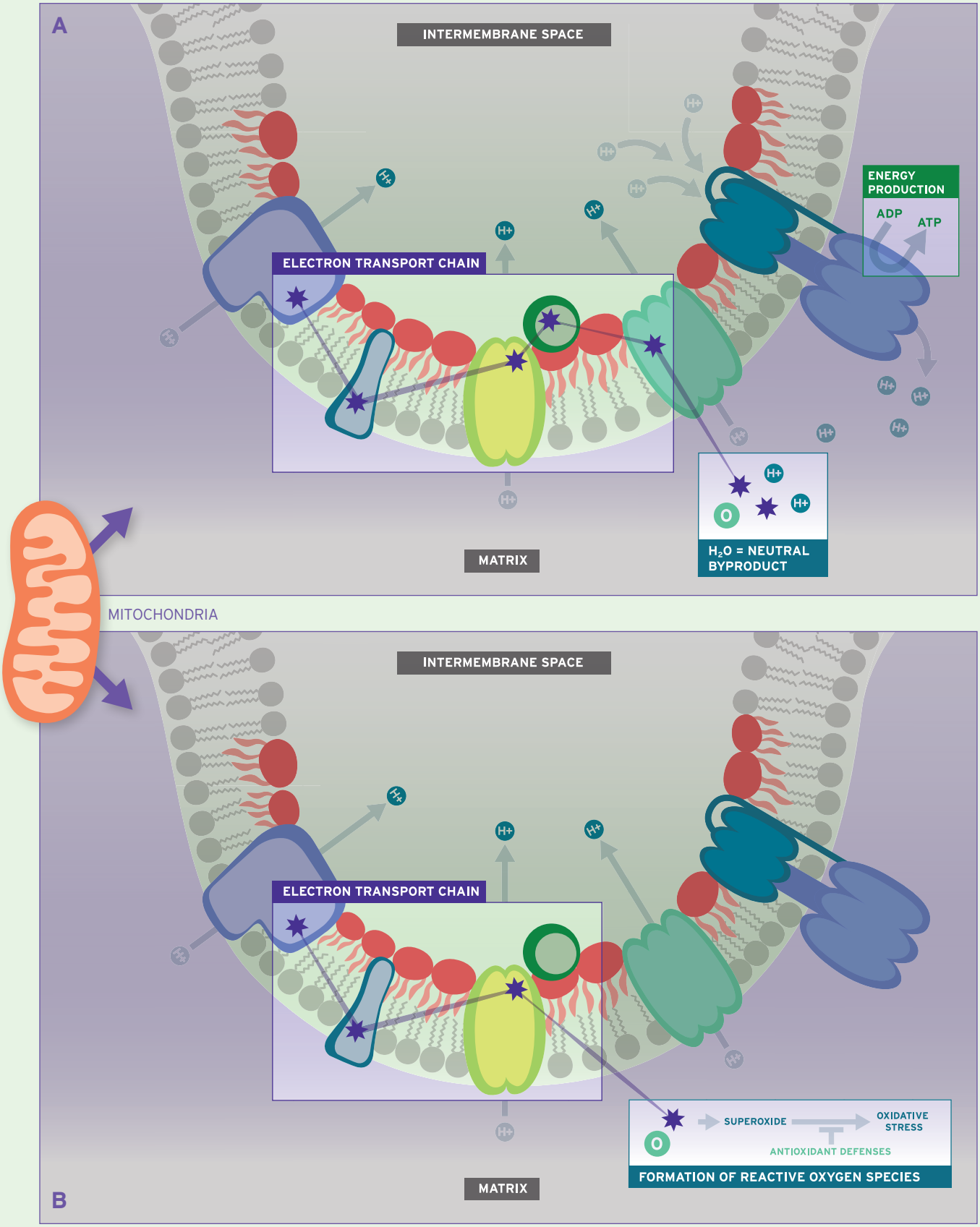


Figure 3. A) Shows cellular respiration within the mitochondria. **B)** Depicts the production of ROS within the mitochondria. Purple lines show the flow of electrons and green arrows show the flow of hydrogen ions.

product of glucose processing in the cytoplasm, is metabolized by mitochondria, a type of cellular organelle, to form acetyl-CoA. Electron donors generated from acetyl-CoA processing provide electrons to the electron transport chain (ETC), a string of membrane-bound proteins and channel proteins located on the inner membrane of the mitochondrion. The movement of electrons along the ETC transports hydrogen ions from the matrix into the intermembrane space. The enzyme ATP synthase is a channel protein also located on the inner membrane. The flow of hydrogen ions through ATP synthase back into the matrix drives ATP production. Oxygen and hydrogen ions are used to absorb the electrons from the ETC to form water, the neutral byproduct of cellular respiration **(Figure 3A)**.[8]

Clinical studies have revealed that oxygen, even in the most ideal circumstances, can sometimes attract electrons away from the ETC.[27] The absorption of an extra electron into a binary oxygen molecule creates superoxide, a form of reactive oxygen species (ROS, **Figure 3B**).[28] Most of the ROS formed during normoxia is neutralized to hydrogen peroxide by superoxide dismutase (SOD), an antioxidant enzyme in the mitochondria and the cytoplasm.[29] Hydrogen peroxide is further processed into oxygen and water by other antioxidant mechanisms, such as the oxidation of glutathione and decomposition by the enzyme catalase.[30,31]

ROS formation occurs more often when oxygen is overabundant, such as during hyperoxia. Hyperoxia and hyperoxemia are not natural phenomena. High concentrations of oxygen in the body only occur with oxygen supplementation.[8,32] The high concentrations of superoxide that form during hyperoxia can overwhelm a cell's antioxidant defenses.[28,33] Molecules of hydrogen peroxide that circumvent antioxidant mechanisms react with metal ions (e.g. iron) to form hydroxyl ions, a highly reactive form of ROS. ROS formed during hyperoxia can react with and damage biomolecules, such as nucleic acids, lipids, and proteins.[8,34]

The rate of ATP production during cellular respiration decreases during periods of hypoxia, when oxygen concentrations are low. Accumulating evidence suggests that the properties of the ETC change during hypoxia to permit some cellular respiration to continue.[33] ROS are also formed during periods of minimal oxygen, but in this context ROS activate stress response pathways that further promote survival. If the oxygen supply is not restored, cell death pathways may be initiated.[8,33]

While the restoration of normoxia has clear, long-term benefits for an oxygen-starved cell, reoxygenation can cause short-term oxidative stress and cellular damage. Recent studies suggest that as the supply of oxygen returns to near-normoxic levels, adaptive changes in the ETC permit more ROS to be produced. A burst of ROS has been found to occur following the restoration of oxygen delivery.[33,35,36] The amount of ROS that is produced is dependent on the amount of time cells spend in hypoxia.[31]

The Role of Oxygen in Vasodilation

Beyond its use for energy production in the cell, oxygen has also been found to function as a vasodilator in the pulmonary vasculature.[9] Oxygen-mediated vasodilation plays a central role in the cardiopulmonary transition at birth as the newborn goes from the womb's hypoxic environment (32-35 mm Hg) to the relatively hyperoxic environment of extrauterine life (90-100 mm Hg).[37,38] Hypoxic vasoconstriction is an adaptive process in newborns that helps the body maximize gas exchange in areas of the lung that are well-ventilated. Excessive hypoxic vasoconstriction can increase pulmonary vascular resistance (PVR) and reduce cardiac output. Oxygen is used to help relieve some of this vasoconstriction and improve tissue oxygenation.[39,40] However, one study in fetal lambs by Lakshminrusimha and colleagues showed that the vasodilatory effect of oxygen is only evident up to a partial pressure of oxygen (pO_2) of 52.5 mm Hg. Higher serum oxygen levels (up to a pO_2 of 600 mm Hg) did not promote further dilation of pulmonary arterioles. While this preclinical data in lambs may not necessarily translate to a similar physiological response in humans, the hemoglobin dissociation curve shows that ~80% of hemoglobin molecules are saturated with a pO_2 of ~50 mm Hg.[41] Taken together, these findings may suggest that most of the vasodilatory effect of oxygen occurs immediately following recovery from an episode of hypoxia when hemoglobin molecules are nearing full saturation.

Efforts to Define the Appropriate Oxygenation Saturation Range in Neonates

> "The exact definition of how much oxygen should be given to neonates is unclear. No one is sure what the actual range should be."
>
> –Amy R. Koehn, PhD, NNP-BC

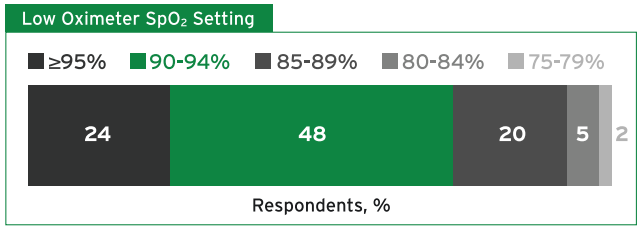
Oxygen is a drug. While almost all drugs have clearly defined guidelines for their use, oxygen does not. With the exception of the Neonatal Resuscitation Program protocol,

used to guide resuscitation after birth, there are no clear guidelines for oxygen use in neonates.[42] Moreover, there is no consensus of what arterial oxygen saturation range is required to achieve optimal outcomes in neonates with respiratory distress.[43]

This lack of consensus in the field, regarding acceptable limits for SpO_2, has resulted in a wide variation in oxygen use. It has also fostered differing opinions as to what constitutes a safe high- and/or low-saturation target range.[44] In one 2015-2016 survey, 492 neonatologists were asked about their goal parameters for pre-ductal SpO_2 during treatment of a neonate with persistent pulmonary hypertension of the newborn (PPHN). These physicians reported a wide range of targets. The most commonly reported target range (39% of respondents) was a lower SpO_2 limit of >95% and no upper target limit.[45]

There is also a lack of consensus on SpO_2 target limits among neonatal nurses. The ranges most commonly reported by neonatal nurses at the 2017 NANN Symposium involved a lower SpO_2 target of 90%-94% (48% of respondents, **Figure 4A**) and a high SpO_2 target between 95% and 99% (59% of respondents, **Figure 4B**). These data illustrate the lack of consensus that exists concerning oxygen saturation ranges among clinicians in NICUs as well as in regard to support efforts to standardize oxygen management.

A. What low target parameter of pre-ductal SpO_2 do you use in the management of PPHN? (n=128)



B. What high target parameter of pre-ductal SpO_2 do you use in the management of PPHN? (n=158)

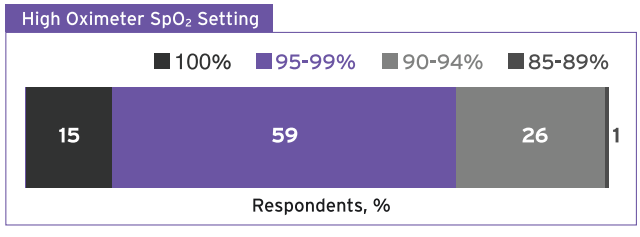


Figure 4. NANN symposium 2017 attendees were asked what they used as a **A)** low- or **B)** high-target range of pre-ductal SpO_2 for the management of PPHN. The range of responses is shown above.

How Is Oxygen Use in the NICU Changing?

Persistent pulmonary hypertension of the newborn (PPHN) can be a challenging disease to manage. It can arise when the cardiopulmonary transition does not successfully progress in a newborn, often due to lung disease and/or hypoxic respiratory failure. Oxygen is commonly used to improve oxygenation with PPHN.[37] The use of oxygen in this patient population was assessed by polling among attendees at the 2017 NANN symposium, as well as at similarly-sponsored NANN symposia in 2014 and 2015. Results from the audiences in 2014, 2015, and 2017 were compared to examine whether perceptions of oxygen use had changed over time.

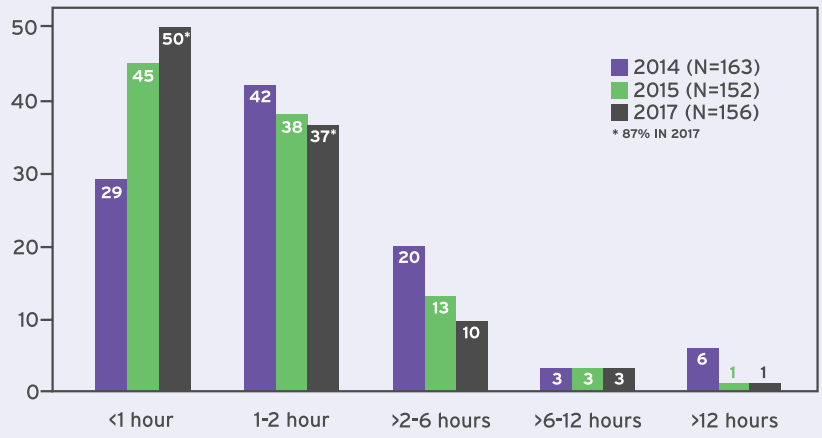
Results from these 3 audiences, when taken together, suggest that attitudes surrounding oxygen usage did in fact change over time. In the past 3 years, attendees have become more willing to consider alternative treatments to fraction of inspired oxygen, FiO_2=0.60 earlier in near-term and term neonates with PPHN **(Figure 5A)**, with half of 2017 attendees now waiting less than 1 hour compared to just 29% in 2014. 87% of 2017 attendees were willing to wait at most 2 hours before considering additional options for a near-term or term neonate with hypoxic respiratory failure (HRF)/PPHN. When the same question was asked about preterm infants, respondents took even less time, with 67% waiting less than one hour to consider alternative options **(data not shown)**.

Over time, fewer respondents were willing to permit near-term and term neonates with HRF/PPHN to remain on an FiO_2 of 1.0 before considering additional interventions **(Figure 5B)**. Regardless of whether a neonate is near-term or preterm, over 95% of respondents were unwilling to use an FiO_2 of 1.0 for more than one hour if at all in 2017 **(Figure 5B and data not shown)**.

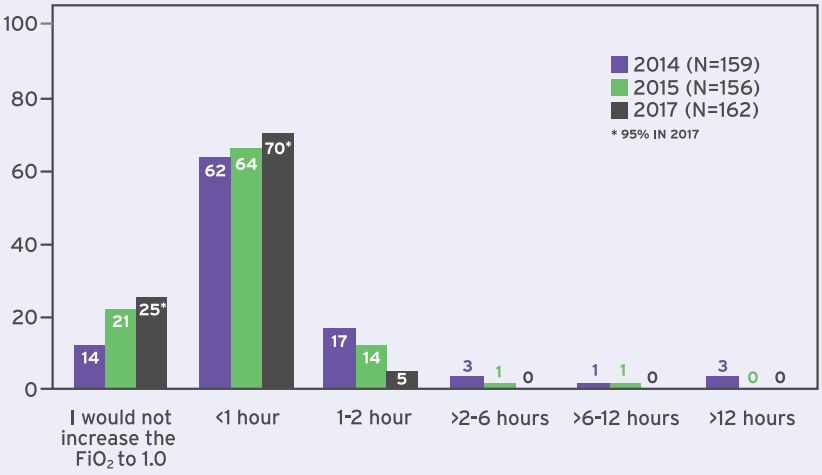
These attitudes surrounding reduced length of use also extended to a reduction in the concentration of oxygen used. Most attendees were unwilling to use high levels of inspired oxygen (FiO_2 > 0.70). In 2017, 84% of respondents would not exceed an FiO_2 of 0.70 to obtain adequate oxygenation (arterial partial pressure of oxygen, PaO_2 >60 mm Hg) in a near-term infant with HRF/PPHN. This number jumps to 94% when preterm infants with HRF/PPHN are considered **(Figure 5C)**.

Subanalyses of all collected ARS data comparing different unit types (Levels 1-4) and primary profession in the NICU (e.g., neonatal nurses and nurse practitioners) showed no significant differences in audience response to the questions examining oxygen use (data not shown). This suggests that the shift in attitudes surrounding oxygen usage may be occurring across all professions and unit types in the NICU.

A. How long do you typically permit near-term/term neonates with HRF/PPHN to remain on an FiO_2 of 0.60 before considering additional interventions?



B. How long do you typically permit near-term/term neonates with HRF/PPHN to remain on an FiO_2 of 1.0 before considering additional interventions?



C. What would you consider to be a maximal amount of FiO_2 to obtain adequate oxygenation (PaO_2 >60 mm Hg) for a preterm or a near-term/term infant with HRF/PPHN?

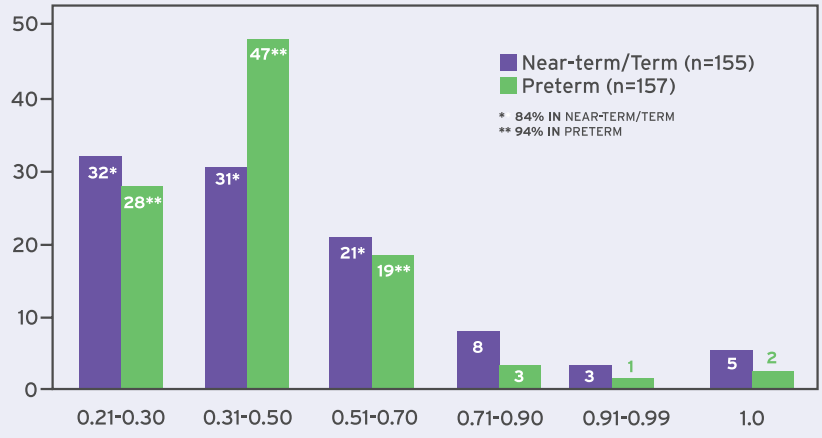


Figure 5. Graphs illustrate the audience response at the 2014, 2015, and 2017 NANN Symposia. **A)** Shows changing attitudes surrounding usage of FiO_2=0.60 near-term/term neonates with PPHN. **B)** Illustrates shifting views concerning usage of FiO_2=1.0 near-term/term neonates with PPHN. **C)** Compares what 2017 NANN symposium attendees consider to be a maximal amount of FiO_2 to obtain adequate oxygenation for a preterm infant relative to a near-term/term infant with PPHN.

Recently, 5 multicenter studies attempted to identify a safe oxygen saturation range for preterm neonates (<28 weeks gestational age) by examining the clinical outcome of 2 cohorts of neonates exposed to high (91%-95%) and low (85%-89%) SpO_2 target ranges. Oxygen saturation targets in all of these studies were maintained until 36 weeks of postmenstrual age. A meta-analysis of these data (for 4911 infants across the 5 studies) called the Neonatal Oxygenation Prospective Meta-Analysis, or NeOProM, found that use of high SpO_2 targets resulted in higher levels of retinopathy of prematurity (ROP) while use of lower targets were possibly associated with more deaths and a greater incidence of necrotizing enterocolitis.[46] While such meta-analyses may be misleading due to biases in search methodology, study selection, and the preference to publish positive results, when used properly, can help increase the power of multiple studies to focus on a single effect.[47] The results from the NeOProM demonstrate the difficulty clinicians face when trying to standardize oxygen management. They suggest that both high and low SpO_2 target ranges put newborns at risk for potential long-term sequelae. A "one size fits all" approach to oxygen saturation targeting will likely not be possible for neonates in critical care.[46]

One variable that interferes with the ability of studies — such as those included in NeOProM— to identify a safe oxygen saturation range is the varying and shifting oxygen demands of the study participants. The oxygen saturation target ranges in these studies were fixed and may not have been clinically appropriate for certain subjects during certain periods of the studies. The authors of two recent meta-analyses of these studies noted that other factors such as gestational age, growth status, and pulmonary hypertension can influence the sensitivity of neonates to insufficient and/or excessive oxygenation. They concluded that certain fixed ranges may not be ideal for all patients.[46,48] On one hand, it is important to standardize clinical practice when variability exists in a way that may impact patients, but on the other, standardization of oxygen delivery without consideration of oxygen demand may affect the overall effectiveness of the protocol.

The Challenge of Maintaining Normoxia in Neonates with Respiratory Distress

Some NICUs are attempting to develop a local policy for oxygen saturation target ranges. In one 2015-2016 survey of neonatologists, only 28% of respondents reported having a specific protocol or clinical practice guideline that the nurses and/or respiratory therapists could use to titrate the FiO_2.[45] Only half of the neonatal nurses at the 2017 NANN symposium were certain that their units audit protocol adherence to SpO_2 targets **(data not shown)**. Furthermore, 79% reported having a unit policy to aggressively wean neonates off FiO_2 as long as minimum SpO_2 targets are maintained (data not shown). Results from a recent study by Hagadorn and colleagues at the NICUs in the Vermont Oxford Network (iNICQ) 2015: Alarm Safety Collaborative, suggest that having a local policy for oximeter alarm settings may reduce unintended oxygen exposure. Neonates treated at iNICQ with high oximeter alarms that were not set to policy were more likely to be exposed to episodes of hyperoxia.[49]

Even with a local policy in place, maintaining oxygen levels within an intended range can be a clinical challenge. A prospective, multicenter cohort study, called AVIOx, examined this issue by documenting the pulse oximeter measurements of 84 preterm neonates (<28 weeks gestation) during their first four weeks of life at 14 centers in three countries. Oxygen saturation measurements were recorded and compared with the oxygen saturation ranges targeted by local policy, which ranged between 83% and 92% for the lower SpO_2 target limits and 92% and 98% for the upper SpO_2 target limits. Neonates in this study spent 48% of the time within the intended range, 16% of the time below the low SpO_2 target, and 36% of the time above the high SpO_2 target. This data suggests that neonates monitored in AVIOx spent more than half of the time out of compliance with local policy.[50]

One approach clinicians have begun to explore to improve the time a neonate in critical care spends within an intended range, involves the use of automation. There are currently three types of automated oxygen delivery systems in development: the closed-loop control of inspired oxygen concentration delivery system, the closed-loop mechanical ventilation system, and the dual-closed-loop control of oxygen delivery system. Multiple studies have shown that automated systems do a better job of keeping patients within a specified target range **(Table 1)**.[51-55] In a recent 2017 study of 16 infants (30 weeks' gestational age), it was found that subjects spent 83%-93% of their time within the target range (91%-95% SpO_2) when using an automated system controlled using a specialized algorithm. This is higher than what was observed in neonates managed with manual controls, who spent only 39%-54% of the time in the specified range.[52] While the specified methods of automation appear promising, additional clinical studies are needed to evaluate whether these approaches are safe and suitable for clinical practice. Moreover, automated systems do not currently ensure that a chosen target range is appropriate for a patient's shifting oxygen demands.

Discussion

Oxygen is essential for life.[8] It is often an appropriate treatment for patients with a low oxygen saturation. However, high levels can be toxic.[17-19] The level or concentration at which it becomes toxic is not well-defined, especially given the current tools available for monitoring and measurement. In recent years, the use of supplemental oxygen has become more judicious, and more care is being taken to manage its delivery.[56] However, these efforts focus on the supply side of oxygen delivery and ignore demand.[13]

Our polling results suggest that oxygen use is changing among neonatal nurses. Polling data from the 2014, 2015, and 2017 NANN Symposia show an increased reluctance to exposing PPHN patients to high concentrations of oxygen. In addition, neonatal nurses are considering alternative treatments to oxygen earlier, suggesting that they are not comfortable with prolonged exposure.

It is unclear whether these improvements in neonatal care are due to changes in local policy. While the majority of 2017 NANN respondents work in NICUs with policies for oxygen use, only half of all respondents are certain that these protocols are being followed. One recent study showed that adherence to local policies can reduce unintended oxygen exposure.[49] Future developments in automated oxygen delivery may help clinicians meet the requirements of local policy and improve patient outcomes.[51-55]

But are improvements in local policy sufficient for ensuring proper oxygen use?

Given the variables that exist in neonates requiring respiratory support, identification of an ideal oxygen saturation range for a given population may be difficult if the supply and demand for oxygen are not well-matched.[13] The oxygen demands of the patient can change during the course of treatment dependent on pathological conditions and the treatments. In addition, patient characteristics and pathological conditions can influence a neonate's sensitivity to insufficient and/or excessive oxygenation.[13,21-24] While there are clear benefits to establishing a local policy for oxygen use in the NICU, the appropriate oxygenation target range for a patient may be best determined by the clinician.

Attempts to standardize oxygen management in newborns are focused on managing the oxygen supply.[46,48] These efforts to delineate a safe oxygenation range can be difficult. While clinicians do an excellent job monitoring and managing oxygen supply, oxygen demand is often ignored. Even if clinicians regularly monitored demand, matching the supply of oxygen to the patient's ever-changing demand would be a challenge. Each patient and every moment for each patient is different. Hyperoxia and hypoxia probably constitute a continuum for patients in critical care.[13] It remains the clinician's burden to manage oxygenation using their best judgement. Clinical practice is evolving. In time, improvements in knowledge and technology may clarify safer oxygen use and help resolve this oxygen saturation conundrum.

Study	Gestational Age, Weeks	Subjects	Oxygen Saturation Range	Manual Time in Range, %	Automated Time in Range, %
Plottier et al, 2017[45,51]	26-30	20	<90%	19 (12-27)	0
			90%-94% (target)	55 (46-60)	0
			>94%	25 (23-35)	0
		20	<91%	0	14 (7.8-19)
			91%-95% (target)	0	78 (75-87)
			>95%	0	5.1 (3.1-6.9)
Dargaville et al, 2017[46, 52]	30	16	<91%	10 (7.2-17)	3.7 (3.1-4.2)
			91%-95% (target)	49.2 (39.3-54.1)	91.1 (83.1-92.6)
			>95%	38 (32-54)	4.8 (3.9-13)
Van Kaam et al, 2015[47, 53]	26	40	<89%	21 ±8	17 ±11
			89%-93% (target)	54 ±16	62 ±17
			>93%	25 ±10	21 ±13
		40	<91%	23 ±9	17 ±10
			91%-95% (target)	58 ±15	62 ±17
			>95%	19 ±8	22 ±13
Clarke et al, 2015[48,54]	<32	16	<88%	23.7 ±14.4	25.3 ±15.4
			88%-92% (target)	34.6 ±28.5	38.3 ±29.3
			>92%	45.8 (25.5-59.3)	40.2 (14.8-54.4)
Claure et al, 2009[49,55]	25	16	<88%	27 ±9	33 ±7
			88%-95% (target)	42 ±9	58 ±10
			>95%	31 ±8	9 ±10

Table 1. Table summarizing several studies that compared experimental automated oxygen saturation monitoring and delivery with manual controls.

References

1. Cook C. Retrolental fibroplasia. *Postgrad Med J*. 1957;33(380):260-265.
2. Anderson WR, Strickland MB, Tsai SH, Haglin JJ. Light microscopic and ultrastructural study of the adverse effects of oxygen therapy on the neonate lung. *Am J Pathol*. 1973;73(2):327-348.
3. Greenough A. Bronchopulmonary dysplasia: early diagnosis, prophylaxis, and treatment. *Arch Dis Child*. 1990;65(10 Spec No):1082-1088.
4. Kilpatrick B, Slinger P. Lung protective strategies in anaesthesia. *Br J Anaesth*. 2010; 105 Suppl 1:i108-116.
5. Nash G, Blennerhassett JB, Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artificial ventilation. *N Engl J Med*. 1967;276(7):368-374.
6. Delaney C, Cornfield DN. Risk factors for persistent pulmonary hypertension of the newborn. *Pulm Circ*. 2012;2(1):15-20.
7. Hermansen CL, Lorah KN. Respiratory distress in the newborn. *Am Fam Physician*. 2007;76(7):987-994.
8. Kulkarni AC, Kuppusamy P, Parinandi N. Oxygen, the lead actor in the pathophysiologic drama: enactment of the trinity of normoxia, hypoxia, and hyperoxia in disease and therapy. *Antioxid Redox Signal*. 2007;9(10):1717-1730.
9. Cornfield DN, Reeve HL, Tolarova S, Weir EK, Archer S. Oxygen causes fetal pulmonary vasodilation through activation of a calcium-dependent potassium channel. *Proc Natl Acad Sci U S A*.1996;93(15): 8089-8094.
10. Ahearne CE, Boylan GB, Murray DM. Short and long term prognosis in perinatal asphyxia: an update. *World J Clin Pediatr*. 2016;5(1):67-74.
11. Michiels C. Physiological and pathological responses to hypoxia. *Am J Pathol*. 2004;164(6):1875-1882.
12. Lakshminrusimha S, Manja V, Mathew B, Suresh GK. Oxygen targeting in preterm infants: a physiological interpretation. *J Perinatol*. 2015;35(1):8-15.
13. Dudell G, Cornish JD, Bartlett RH. What constitutes adequate oxygenation? *Pediatrics*. 1990;85(1):39-41.
14. Bonnaire P. Des Inhalations d'Oxygenène Chez les Nouveau-Nès. *Journ de Med*. 1891:312-314.
15. Rotch T. Pediatrics: The Hygienic and Medical Treatment of Children. Philadelphia, PA: *J. B. Lippincott Company*; 1906.
16. Grainge C. Breath of life: the evolution of oxygen therapy. *J R Soc Med*. 2004;97(10):489-493.
17. Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics*. 2004;113(2):394-396.
18. Campbell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia: a clinical approach. *Med J Aust*. 1951;2(2):48-50.
19. Avery ME. Recent increase in mortality from hyaline membrane disease. *J Pediatr*. 1960;57:553-559.
20. Dawson JA, Davis PG, O'Donnell CP, Kamlin CO, Morley CJ. Pulse oximetry for monitoring infants in the delivery room: a review. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(1):F4-7.
21. Gutierrez JA, Theodorou AA. Oxygen delivery and oxygen consumption in pediatric critical care. In: Lucking SE, Maffei FA, Tamburo RF, Thomas NJ., eds. Pediatric Critical Care Study Guide. London: *Springer-Verlag London*; 2012.
22. Bauer J, Hentschel R, Linderkamp O. Effect of sepsis syndrome on neonatal oxygen consumption and energy expenditure. *Pediatrics*. 2002;110(6):e69.
23. Fixler DE, Carrell T, Browne R, Willis K, Miller WW. Oxygen consumption in infants and children during cardiac catheterization under different sedation regimens. *Circulation*. 1974;50(4):788-794.
24. Ferradal SL, Yuki K, Vyas R, et al. Non-invasive assessment of cerebral blood flow and oxygen metabolism in neonates during hypothermic cardiopulmonary bypass: feasibility and clinical implications. *Sci Rep*. 2017;7:44117.
25. Markus T, Hansson S, Amer-Wahlin I, Hellstrom-Westas L, Saugstad OD, Ley D. Cerebral inflammatory response after fetal asphyxia and hyperoxic resuscitation in newborn sheep. *Pediatr Res*. 2007;62(1):71-77.
26. Goldsmith JP, Karotkin E. Assisted Ventilation of the Neonate. 5th ed. St. Louis, MO: *Elsevier Saunders*; 2011.
27. McCord JM. The evolution of free radicals and oxidative stress. *Am J Med*. 2000;108(8):652-659.
28. Turrens JF. Mitochondrial formation of reactive oxygen species. *J Physiol*. 2003;552(Pt 2):335-344.
29. McCord JM, Fridovich I. The utility of superoxide dismutase in studying free radical reactions. I. Radicals generated by the interaction of sulfite, dimethyl sulfoxide, and oxygen. *J Biol Chem*. 1969;244(22):6056-6063.
30. White CW, Mimmack RF, Repine JE. Accumulation of lung tissue oxidized glutathione (GSSG) as a marker of oxidant induced lung injury. *Chest*. 1986;89(3 Suppl):111S-113S.
31. Switala J, Loewen PC. Diversity of properties among catalases. *Arch Biochem Biophys*.2002;401(2): 145-154.
32. Klinger G, Beyene J, Shah P, Perlman M. Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? *Arch Dis Child Fetal Neonatal Ed*. 2005;90(1):F49-52.

33. Li C, Jackson RM. Reactive species mechanisms of cellular hypoxia-reoxygenation injury. *Am J Physiol Cell Physiol*. 2002;282(2):C227-241.

34. Forstermann U. Oxidative stress in vascular disease: causes, defense mechanisms and potential therapies. *Nat Clin Pract Cardiovasc Med*. 2008;5(6):338-349.

35. Zweier JL, Broderick R, Kuppusamy P, Thompson-Gorman S, Lutty GA. Determination of the mechanism of free radical generation in human aortic endothelial cells exposed to anoxia and reoxygenation. *J Biol Chem*. 1994;269(39):24156-24162.

36. Torres-Cuevas I, Parra-Llorca A, Sanchez-Illana A, et al. Oxygen and oxidative stress in the perinatal period. *Redox Biol*. 2017;12:674-681.

37. Vali P, Lakshminrusimha S. The fetus can teach us: oxygen and the pulmonary vasculature. *Children (Basel)*. 2017;4(8): 67.

38. Teitel DF, Iwamoto HS, Rudolph AM. Changes in the pulmonary circulation during birth-related events. *Pediatr Res*. 1990;27(4 Pt 1):372-378.

39. Jain A, McNamara PJ. Persistent pulmonary hypertension of the newborn: advances in diagnosis and treatment. *Semin Fetal Neonatal Med*. 2015;20(4):262-271.

40. Farrow KN, Wedgwood S, Lee KJ, et al. Mitochondrial oxidant stress increases PDE5 activity in persistent pulmonary hypertension of the newborn. *Respir Physiol Neurobio*l. 2010;174(3):272-281.

41. Lakshminrusimha S, Swartz DD, Gugino SF, et al. Oxygen concentration and pulmonary hemodynamics in newborn lambs with pulmonary hypertension. *Pediatr Res*. 2009;66(5):539-544.

42. Perlman JM, Wyllie J, Kattwinkel J, et al. Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Pediatrics*. 2010;126(5):e1319-1344.

43. Vento M. Oxygen supplementation in the neonatal period: changing the paradigm. *Neonatology*. 2014;105(4):323-331.

44. Sola A, Golombek SG, Montes Bueno MT, et al. Safe oxygen saturation targeting and monitoring in preterm infants: can we avoid hypoxia and hyperoxia? *Acta Paediatr*. 2014;103(10):1009-1018.

45. Alapati D, Jassar R, Shaffer TH. Management of supplemental oxygen for infants with persistent pulmonary hypertension of newborn: a survey. *Am J Perinatol*. 2017;34(3):276-282.

46. Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. *Neonatology*. 2014;105(1):55-63.

47. Walker E, Hernandez AV, Kattan MW. Meta-analysis: its strengths and limitations. *Cleve Clin J Med*. 2008;75(6):431-439.

48. Manja V, Saugstad OD, Lakshminrusimha S. Oxygen saturation targets in preterm infants and outcomes at 18-24 months: a systematic review. *Pediatrics*. 2017;139(1).

49. Hagadorn JI, Sink DW, Buus-Frank ME, et al. Alarm safety and oxygen saturation targets in the Vermont Oxford Network iNICQ 2015 collaborative. *J Perinatol*. 2017;37(3):270-276.

50. Hagadorn JI, Furey AM, Nghiem TH, et al. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics*. 2006;118(4):1574-1582.

51. Plottier GK, Wheeler KI, Ali SK, et al. Clinical evaluation of a novel adaptive algorithm for automated control of oxygen therapy in preterm infants on non-invasive respiratory support. *Arch Dis Child Fetal Neonatal Ed*. 2017;102(1):F37-F43.

52. Dargaville PA, Sadeghi Fathabadi O, Plottier GK, et al. Development and preclinical testing of an adaptive algorithm for automated control of inspired oxygen in the preterm infant. *Arch Dis Child Fetal Neonatal Ed*. 2017;102(1):F31-F36.

53. van Kaam AH, Hummler HD, Wilinska M, et al. Automated versus manual oxygen control with different saturation targets and modes of respiratory support in preterm infants. *J Pediatr*. 2015;167(3): 545-550 e541-542.

54. Clarke A, Yeomans E, Elsayed K, et al. A randomised crossover trial of clinical algorithm for oxygen saturation targeting in preterm infants with frequent desaturation episodes. *Neonatology*. 2015;107(2): 130-136.

55. Claure N, D'Ugard C, Bancalari E. Automated adjustment of inspired oxygen in preterm infants with frequent fluctuations in oxygenation: a pilot clinical trial. *J Pediatr*. 2009;155(5):640-645 e641-642.

56. Sola A, Saldeno YP, Favareto V. Clinical practices in neonatal oxygenation: where have we failed? What can we do? *J Perinatol*. 2008;28 Suppl 1:S28-34.

The contents of this monograph are a written extension of the non-CE symposium discussion hosted and sponsored by Mallinckrodt during the NANN 2017 Annual Conference.