

# 'Resuscitation' of Extremely Preterm and/or Low-Birth-Weight Infants – Time to 'Call It'?

Colm P.F. O'Donnell

The National Maternity Hospital and Our Lady's Children's Hospital, Dublin, Ireland

## Key Words

Preterm infant · Resuscitation · Respiratory support

## Abstract

Since ancient times, various methods have been used to revive apparently stillborn infants; many were of dubious efficacy and had the potential to cause harm. Based largely on studies of acutely asphyxiated term animal models, clinical assessment and positive pressure ventilation have become the cornerstones of neonatal resuscitation over the last 40 years. Over the last 25 years, care of extremely preterm infants in the delivery room has evolved from a policy of indifference to one of increasingly aggressive support. The survival of these infants has improved considerably in recent years; this has not, however, necessarily been due to more aggressive resuscitation. Urban myths have evolved that all extremely preterm infants died before they were intubated, and that all such infants need to immediately intubated or they will quickly die. This has never been true. Clinical assessment of infants at birth is subjective. Also, many techniques used to support preterm infants at birth have not been well studied and there is evidence that they may be harmful. It may thus be argued that many of our well-intentioned resuscitation interventions are of dubious efficacy and have the potential to cause harm. 'Resuscitation' is an emotive term which means 'restoration of life'. Death, thankfully, is a rare presentation in the delivery room. Therefore, concerning neonatal 'resuscitation', it is time to 'call it' something else.

This will allow us to dispassionately distinguish preterm infants who are dead, or nearly dead, from those who are merely at high risk of parenchymal lung disease. We may then be able to refine our interventions and determine what methods of support benefit these infants most.

Copyright © 2008 S. Karger AG, Basel

Resuscitation – restoration to life.

1. Restoration to life. Also fig.

b. spec. Restoration of life or consciousness in one almost or apparently drowned or dead;

c. Restoration to health. rare.

2. Revival, renewal, restoration (of something).

*Oxford English Dictionary*

## Evolution of Neonatal Resuscitation

Attempted revival of apparently lifeless newborn infants has been described since ancient times. Various methods – including slapping, pinching, electrocution, immersion in hot and cold water, and insertion of corn cobs and ravens' beaks into the infant's rectum – have been used, with claims for efficacy made for each [1]. Though subject to the vagaries of fashion over 2,000 years, positive pressure ventilation has become the mainstay of neonatal resuscitation over the last 40 years. This has in large part been due to a series of experiments in which term infants of different species of animals were

## KARGER

Fax +41 61 306 12 34  
E-Mail [karger@karger.ch](mailto:karger@karger.ch)  
[www.karger.com](http://www.karger.com)

© 2008 S. Karger AG, Basel  
1661–7800/08/0934–0295\$24.50/0

Accessible online at:  
[www.karger.com/neo](http://www.karger.com/neo)

Colm P.F. O'Donnell, MB, MRCPI, MRCPC, FRACP, PhD  
Neonatal Intensive Care Unit  
The National Maternity Hospital  
Hollis Street, Dublin 2 (Ireland)  
Tel. +353 1 637 3100, Fax +353 1 661 4623, E-Mail [codonnell@nmh.ie](mailto:codonnell@nmh.ie)

subjected to an acute and total asphyxial insult (in the seminal experiment a term Rhesus monkey had its umbilical cord ligated and head covered with a saline-filled condom to prevent breathing) [2]. Initially these animals made vigorous breathing efforts, which then ceased and were followed by agonal gasping as they became increasingly acidaemic, bradycardic and hypotensive. The animals progressed inexorably toward death unless they were given intermittent positive pressure ventilation (IPPV) with an oxygen-rich gas through an endotracheal tube (ETT). Endotracheal ventilation prompted a rapid increase in heart rate, which was followed by an increase in systemic blood pressure and pH, visible improvement in colour and a return of gasping respiration. IPPV was accepted largely in the absence of human studies; the only randomised study evaluating its use reporting that endotracheal ventilation and placement in a hyperbaric oxygen chamber 'are equally effective methods of infant resuscitation' [3]. Over the last 20 years specific courses in neonatal resuscitation based on these techniques have been designed, refined and taught to millions of health-care providers around the world [4, 5]. Over the last 10 years the Neonatal Subcommittee of the International Liaison Committee on Resuscitation has issued guidelines for neonatal resuscitation [6] and serially evaluated the evidence available to support current recommendations [7, 8]. The key elements of neonatal resuscitation are clinical assessment to determine 'need' for intervention (while taking measures to keep the infant warm) and positive pressure ventilation for those deemed to 'need' it. In contrast to adult resuscitation less emphasis is placed on circulatory support, as it is infrequently used and, even when it is, circulation is rarely the primary problem.

### Guidelines for Resuscitation of Preterm Infants

Guidelines for neonatal resuscitation state that every infant's 'need' for resuscitation should be determined based on clinical assessments of their breathing, heart rate and colour [4–7]. If one or more of these assessments are unsatisfactory, positive pressure ventilation is given by mask or ETT. Initially, few distinctions were made in techniques that may be desirable for preterm infants, other than to note that the incidence of perinatal depression amongst preterm infants was markedly increased and that some practitioners advised early intubation of all extremely preterm infants [6, 7]. The advice offered was based on experience with little evidence to support the methods advocated [9]. More recent publications state

**Table 1.** Mortality rates of premature infants of the Sarah Morris Hospital between the years 1922–1940 based on weight and time of death

Birth weight	Total admissions	Number graduated	Deceased			Survived %
			first 24 h	24–48 h	after 48 h	
<1,000 g	247	32	136	28	51	12.95
1,001–1,250 g	286	110	89	34	53	38.46

Adapted from Hess and Lundeen [13, p. 263, table XVIII].

that animal experiments indicate that preterm lungs are more prone to injury and that the application of positive end-expiratory pressure may be beneficial [8]. They further state that while continuous positive airway pressure (CPAP) helps stabilise and improve lung function in sick newborns, there is insufficient evidence to support or refute its routine use during or immediately after resuscitation in the delivery room (DR).

### Epidemiology of Respiratory Support of Extremely Preterm Infants in the DR

The majority of extremely preterm/extremely low birth weight (ELBW; <1,000 g) infants receive respiratory support in the DR (97% of 27–28 weeks' gestation infants born in the UK in 1998–2000) [10]. These infants are commonly intubated at birth. In 2000–2003 in Australia and New Zealand, 85% of infants <750 g and 63% of infants <750–999 g intubated in the DR [11]. In 2004, the proportion of infants <1,500 g intubated in the DR born at centres contributing to the Vermont-Oxford Neonatal Network was also high and inversely related to birth weight (81% of infants <750 g; 74% of infants 751–1,000 g; 49% of infants 1,001–1,499 g) [12].

### 'Resuscitation' and Death in the DR

Perhaps many extremely preterm/ELBW infants are intubated in the DR for resuscitation, i.e. to avoid imminent death. But how likely and imminent is death for infants not intubated at birth? For infants born in the modern era, it is not clear. However, insights may be gleaned from history.

**Table 2.** Time of death and neonatal mortality overall and by gender for inborn infants with birth weights 751–1,000 g admitted to 10 premature nurseries in New York City in 1955–1957

	Number of infants										Total
	15–29 min	30–59 min	1st h	2–5 h	6–11 h	12–17 h	18–23 h	1st day	2–6 days	7–28 days	
Males (n = 173)	0 (0)	5 (3)	15 (9)	46 (27)	25 (14)	13 (8)	11 (6)	12 (7)	20 (12)	9 (5)	156 (90)
Females (n = 167)	0 (0)	1 (1)	9 (5)	22 (13)	20 (12)	13 (8)	7 (4)	15 (9)	22 (13)	10 (6)	119 (72)
Total (n = 340)	0 (0)	6 (2)	24 (7)	68 (20)	45 (13)	26 (8)	18 (5)	27 (8)	42 (12)	19 (6)	275 (81)

Adapted from Silverman [14]. Figures in parentheses indicate percentages.

Hess and Lundeen reported the mortality rates for infants admitted to the ‘premature station’ of the Sarah Morris Hospital in Chicago 1922–1940 (table 1) [13]. They reported all infants admitted and did not distinguish between infants born at the hospital (inborn) and outborn infants. No infant was intubated for respiratory support. Among infants with birth weight <1,000 g, 55% infants died at <24 h, 11% died between 24 and 48 h, 21% died before ‘graduation’ and 13% ‘graduated’ from the nursery.

Silverman subsequently reported the neonatal (<28-day) mortality rate and time of death for 7,530 infants admitted to 10 ‘premature centers’ in New York City in 1955–1957 (table 2) [14]. Amongst these infants were 335 with birth weight 501–750 g, and 492 with birth weight 751–1,000 g. Three hundred and twenty-eight (98%) infants 501–750 g died in the first 28 days of life, as compared with 383 (78%) of infants 751–1,000 g (overall mortality 711/827 = 86%). The mortality and time of death of inborn infants weighing 751–1,000 g overall and according to gender is shown in table 2. No infant died within 30 min of birth. Boys died more commonly and more quickly than the girls.

McDonald et al. [15] reported the proportion of infants born at a single hospital in 1970–1975 who ‘required >1 min of positive pressure ventilation before sustained respiration occurred’ (table 3). The proportion who received PPV was inversely related to maturity and was 28.4% amongst infants of 27–28 weeks. Perhaps a more interesting way to look at these data is that in the early 1970s, 71% of infants 27–28 weeks had sustained breathing after birth without PPV, a stark contrast with the UK a quarter of a century later [10].

The relevance of these historical data to extremely preterm infants born today is limited. In the earlier cohorts more mature, growth-restricted infants are likely over-represented; and infants who were born alive but registered as still-births (or simply not registered) are likely

**Table 3.** Numbers and proportion of infants born at Magee Women’s Hospital, Philadelphia, in 1970–1975 who received >1 min of positive pressure ventilation before sustained respiration occurred

Gestation	Infants	Asphyxia	Rate, %
Overall	32,837	348	1.1
27–28 weeks	67	19	28.4
<27 weeks	106	66	62.3

Adapted from MacDonald et al. [15].

not included [13, 14]. One could reasonably speculate, therefore, that the survival of such infants in these historical cohorts is an overestimate of their survival in that era. Their survival, however, likely underestimates survival today, as neonatal mortality rates have fallen overall. Also the condition of infants at birth today is likely to be better than in the 1970s due to improvements, amongst other things, in perinatal care. For example, for the cohort born in 1970–1975, the rate of antenatal steroid use, epidural anaesthesia, breech vaginal and caesarean section delivery was 0, 0, 4 and 8.4% respectively [15]. Speculation aside, the historical and more recent data do reveal some interesting facts. Firstly, even 50–80 years ago, not all extremely preterm/ELBW newborns died without immediate respiratory support. Secondly, of those that died, many did not die within minutes of birth. Thirdly, many infants did not receive respiratory support before sustained breathing ensued. It is, thus, an urban myth that all extremely preterm and ELBW infants died before they were intubated. It is also an urban myth that all such infants will quickly die in the DR if they are not intubated.

## Respiratory Support for Extremely Preterm/ELBW Infants

Frequent early death from respiratory failure among infants born prematurely was reported more than 4,000 years ago [1]. Mortality among premature infants who developed hyaline membrane disease remained high through the 1950s and 1960s. The first evidence from randomised studies that IPPV could benefit infants came in 1961 when Wright et al. [16] reported that more infants with tetanus neonatorum survived if they were treated with IPPV (14/25 vs. 4/25). In 1967, Reid et al. [17] reported that more infants with respiratory distress syndrome (RDS) survived if they were randomised to IPPV than to 'a modified Usher regimen' (O<sub>2</sub> and IV NaHCO<sub>3</sub> and glucose) between 3 and 6 h of age (8/10 survivors compared to 2/10). In 1970, Murdock et al. [18] reported the results of a randomised comparison of ventilation with various different machines (including a negative pressure ventilator) and supplemental ambient O<sub>2</sub> for 221 outborn infants with RDS. Survival increased significantly amongst ventilated infants  $\geq 33$  weeks' gestation (36/92 vs. 6/26); no difference was seen amongst less mature infants. Also in 1970, Llewellyn et al. [19] reported that, while fewer infants were subsequently intubated for PPV if they were randomised to PPV via a tightly fitting face mask rather than supplemental ambient O<sub>2</sub> (13/22 vs. 20/22), their survival rates were not significantly different (8 vs. 12). Of note, infants weighing <1,000 g at birth were excluded from all of these studies [17–19].

In 1971, Gregory et al. [20] described the use of CPAP in a case series of 20 infants with established severe idiopathic RDS (PaO<sub>2</sub> <50 mm Hg in 100% O<sub>2</sub>; or frequent episodes of apnoea, cyanosis and bradycardia in 70–100% O<sub>2</sub>). Pressures of 6–12 mm Hg ( $\approx$  8–16 cm H<sub>2</sub>O) were given to 18 infants via an ETT and to 2 infants via a pressure chamber enclosing the head. Sixteen (80%) infants survived – including 7 of 10 infants who weighed 930–1,500 g and the authors reported that 'we should have expected less than 25% of our infants to survive'. Subsequently different devices and interfaces were developed with which CPAP could be delivered [21, 22].

In 1982, Drew reported a comparison routine intubation to 'selective' intubation for infants <1,500 g performed at a single centre in 1978–1979 [23]. More infants in the routine intubation group survived (53/69, 77%) than in the selectively intubated group (49/96, 51%). This study however is difficult to interpret principally because of the unequal care given to the groups [24]. Junior staff were more often responsible for the selective intubation

group, while infants in the routine intubation group were invariably cared for by a neonatologist (indeed, infants in the intubation group were excluded from the analysis if the neonatologist and resuscitation team were not present at delivery). The better outcome of the routinely intubated group may thus have been due to more skilled care or to exclusion of some high-risk infants.

Endogenous surfactant deficiency was known to be a contributory factor to RDS as early as 1959 [25]. Between the 1970s and 1990s, exogenous surfactants were prepared, given to animals, subsequently given to infants and, ultimately, evaluated in well-designed randomised clinical trials in thousands of infants. Confirming a tremendous advance, these trials demonstrated that surfactant improved survival in infants ventilated for RDS compared to infants ventilated for RDS who did not receive surfactant [26]. Subsequent trials demonstrated that natural surfactants were superior to synthetic preparations [27], that infants with severe RDS benefit from repeated doses of surfactant [28], and that the earlier the surfactant is given, the better the effect [29].

### A Dilemma: The Association between Mechanical Ventilation and Chronic Lung Disease

In the pre-surfactant era, the rate of chronic lung disease (CLD) of prematurity was demonstrated to be substantially higher in institutions in the US which used mechanical ventilation as the primary mode of respiratory support for preterm infants when compared to an institution which favoured the use of nasal CPAP [30]. This association between endotracheal ventilation and CLD was re-affirmed in the post-surfactant era [31]. Though the rates of death and other adverse outcomes were not different between these similar hospitals, the rate of CLD was 4–5 times higher in institutions where the mechanical ventilation and surfactant use was favoured [31]. Several institutions have seen a reduced prevalence of CLD in very preterm infants following increased use of CPAP in preference to mechanical ventilation [32–34].

Clinicians are therefore faced with a dilemma; they would like infants to derive the benefits of surfactant, but are concerned about the negative associations of endotracheal ventilation. This has led to different approaches to respiratory support of preterm infants. One such approach is the so-called 'INSURE' technique, where infants with RDS are briefly intubated to receive surfactant before extubation to CPAP. Studies have evaluated the effect of brief intubation for surfactant delivery followed by

CPAP in infants with RDS, and shown a reduction in the rate of subsequent ventilation [35]. Most of these trials have been unblinded and recruited small numbers of infants [36, 37]; and many infants were of a maturity and size where mechanical ventilation for RDS in institutions favouring CPAP is unusual, and where CLD is an uncommon outcome in general [36, 38]. Though the rate of subsequent ventilation was reduced, no difference was observed in other outcomes. Also, with such a manoeuvre, all infants in the intervention group are intubated and ventilated, if only briefly; one is thus 'intubating to prevent intubation'. Intubation is neither an easy [39–42] nor a benign procedure [42, 43], which many clinicians would prefer to avoid unless it has clear benefits.

A recent randomised trial (the COIN trial) demonstrated that the outcomes for infants 25–28 weeks' gestation with respiratory distress randomised to nasal CPAP or endotracheal IPPV at 5 min of age were similar [44]. Mortality was not different between the groups and the reduced rate of oxygen therapy amongst infants randomised to CPAP seen at 28 days was not sustained at 36 weeks' postmenstrual age. CPAP failed (determined as  $\text{FiO}_2 \geq 0.60$ , and/or  $\text{PaCO}_2 \geq 60$  mm Hg/8 kPa and  $\text{pH} < 7.25$ ) in almost half (46%) of infants randomised to it. Interestingly (and in contrast to other studies) only 70% of infants randomised to intubation received surfactant. The rate of surfactant use was halved in the group randomised to CPAP. Of concern, however, was the higher rate of air leak in those randomised to CPAP (9 vs. 3%). As against that, infants randomised to CPAP spent less time on respiratory support and in hospital [44]. Neurodevelopmental assessment of these infants is ongoing. Would the rate of pneumothorax have been lower if a lower threshold for CPAP failure had been used (e.g.  $\text{FiO}_2 \geq 0.40$ )? Would it have been lower if all infants had received surfactant? All pertinent questions to which there is no answer at present, although there is at least one ongoing trial designed to clarify this dilemma [45]. Points worth noting, though, are that subjective clinical assessment was used to determine eligibility for the COIN trial [44] and also, the infants were 'better' (i.e. had lower mortality and less severe lung disease) than those enrolled in the surfactant trials.

The optimal strategy for respiratory support in extremely preterm/ELBW infants has not been established [45]. Many worry that infants who are not intubated do not benefit from surfactant. However, it is not appropriate to extrapolate the findings from trials of surfactant, where infants in the control group were intubated, to infants who are not intubated. Because infants who are ven-

tilated for RDS do better when given surfactant, it does not necessarily follow that all infants should be intubated for surfactant administration. It is important to establish which respiratory support strategy, if any, is preferable for preterm infants. To do so, further detailed randomised trials are required.

### Why Are Infants Intubated in the DR?

#### *For Resuscitation?*

Perhaps, but death/near death is uncommon. Also, the Dawes' model of neonatal resuscitation was one of an acute severe asphyxial insult in a term infant [2]. Its relevance to many preterm infants today, for example, delivered by caesarean section under regional anaesthesia for maternal pre-eclampsia after antenatal steroids have been given, is highly debatable. A critical point is that these infants are assessed clinically at birth. It is self-evident that these are subjective assessments; worryingly, they appear highly so and may also be inaccurate [46–48]. Perhaps subjectivity in part explains how the majority of infants can be managed without an ETT in the DR (76% of infants  $\leq 1,250$  g, 50% of infants  $\leq 750$  g born at Columbia Presbyterian Hospital, New York, between June 1999 and July 2002 [49]; 75% of infants 25–28 weeks' gestation in Ulm, Germany [50]) in some institutions, while the majority are intubated elsewhere. It appears that a clinician's ability to manage extremely preterm/ELBW infants without intubation in the DR is at least partly related to their belief that it can be done.

#### *For Early Surfactant?*

Perhaps, but in Vermont-Oxford Neonatal Network centres in 1998–2000, although more than 70% were intubated in the DR, only 27% received surfactant there [51]. Interestingly, in a trial which demonstrated that a series of interventions aimed at promoting earlier surfactant delivery that increased surfactant use in the DR and reduced the time taken to give surfactant, the rate of mortality and pneumothorax was not reduced, although severe intraventricular haemorrhage was significantly reduced [52]. Perhaps the benefit of this strategy is now less marked than when the trials of this intervention were originally conducted, as, with the benefit of more widespread antenatal steroid use, the infants are now 'better' at birth.

## 'Neonatal Resuscitation' – A Common Misnomer

I believe that all too frequently we confuse the infants 'need' for resuscitation with our 'need' to resuscitate them. It has been reported that resuscitation is more successful among the newborn than paediatric or adult population. This may well be because we are not comparing like with like. Resuscitation is an intervention applied in other age groups in the presence of respiratory and/or circulatory arrest. In newborns, however, respiratory arrest may be less common than perceived and circulatory arrest appears rare. Therefore it is possible that 'resuscitation' is more successful in newborns because it is applied to many infants who do not 'need' it and are destined to survive without it. It is important to realise that because we apply an intervention (or series of interventions) and the baby survives, the baby does not necessarily survive because of the intervention; they may have survived despite the intervention. It is likely this was the case for infants 'resuscitated' with corn cobs and ravens' beaks.

We should instead try to more clearly distinguish between extremely preterm/ELBW infants who are given treatment soon after birth for parenchymal lung disease which they may have, or be at high risk of developing, and

those who truly require resuscitation. A challenge today is to spot the modern day corn-cobs and ravens' beaks. Randomised trials attempting to answer this important question are ongoing and they deserve our support [53–55]. Other areas needing further research include delaying clamping of the umbilical cord which may reduce the need for subsequent blood transfusion and intraventricular haemorrhage [56], and determining the correct concentration of oxygen for use in the DR [57] and the neonatal unit after stabilisation [58].

## Conclusion

For neonatal 'resuscitation', it is time to 'call it' – that is, it is time to call it what it really is, and therefore call it something different. DR care, perhaps. 'Resuscitation' means 'to bring back from the dead'. Most newly born extremely preterm infants are not dead; they are at high risk of having parenchymal lung disease, which we are not sure how best to treat. This distinction may seem pedantic and irrelevant; it is not. Until we accept that these infants will not quickly die without intubation, it remains difficult to move forward.

## References

- 1 O'Donnell CPF, Gibson AT, Davis PG: Pinching, electrocution, ravens' beaks, and positive pressure ventilation: a brief history of neonatal resuscitation. *Arch Dis Child Fetal Neonatal* Ed 2006;91:F369–F373.
- 2 Dawes GS: *Foetal and Neonatal Physiology: A Comparative Study of the Changes at Birth*. Chicago, Year Book Medical Publishers, 1968.
- 3 Hutchison JH, Kerr MM, Inall JA, Shanks RA: Controlled trials of hyperbaric oxygen and tracheal intubation in asphyxia neonatorum. *Lancet* 1966;1:935–939.
- 4 Kattwinkel J (ed): *Textbook of Neonatal Resuscitation*, ed 5. Elk Grove, American Academy of Pediatrics and American Heart Association, 2006.
- 5 Richmond S (ed): *Newborn Life Support: Resuscitation at Birth*, ed 2. London, Resuscitation Council, 2006.
- 6 Kattwinkel J, Niermeyer S, Nadkarni V, Tibballs J, Phillips B, Zideman D, Van Reempts P, Osmond M: ILCOR advisory statement: resuscitation of the newly born infant. An advisory statement from the Pediatric Working Group of the International Liaison Committee on Resuscitation. *Pediatrics* 1999;103:e56.
- 7 Contributors and Reviewers for the Neonatal Resuscitation Guidelines: International guidelines for neonatal resuscitation: an excerpt from the guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: international consensus on science. *Pediatrics* 2000;106:e29.
- 8 The International Liaison Committee on Resuscitation (ILCOR) consensus on science with treatment recommendations for pediatric and neonatal patients: neonatal resuscitation. *Pediatrics* 2006;117:e978–e998.
- 9 O'Donnell CPF, Davis PG, Morley CJ: Resuscitation of premature infants: what are we doing wrong and can we do better? *Biol Neonate* 2003;84:76–82.
- 10 Confidential Enquiry into Maternal and Child Health (UK). Project 27/28: an enquiry into quality of care and its effect on the survival of babies born at 27–28 weeks. London, The Stationery Office, 2003. <http://www.cemach.org.uk/publications/p2728/mainreport.pdf>.
- 11 Abeywardana S: The report of the Australian and New Zealand Neonatal Network, 2003. Sydney, ANZNN, 2005.
- 12 Vermont Oxford Network: Vermont Oxford Network 2006. <http://www.vtoxord.org/home.aspx>.
- 13 Hess JH, Lundeen EC: *The Premature Infant*. Philadelphia, JB Lippincott, 1941.
- 14 Silverman WA (ed): *Dunham's Premature Infants*, ed 3. New York, Paul B Hoeber, 1961.
- 15 MacDonald HM, Mulligan JC, Allen AC, Taylor PM: Neonatal asphyxia. I. Relationship of obstetric and neonatal complications to neonatal mortality in 38,405 consecutive deliveries. *J Pediatr* 1980;96:898–902.
- 16 Wright R, Sykes MK, Jackson BG, Mann NM, Adams EB: Intermittent positive-pressure respiration in tetanus neonatorum. *Lancet* 1961;2:678–680.
- 17 Reid DH, Tunstall ME, Mitchell RG: A controlled trial of artificial respiration in the respiratory-distress syndrome of the newborn. *Lancet* 1967;1:532–533.
- 18 Murdock AI, Linsao L, Reid MM, Sutton MD, Tilak KS, Ulan OA, Swyer PR: Mechanical ventilation in the respiratory distress syndrome: a controlled trial. *Arch Dis Child* 1970;45:624–633.
- 19 Llewellyn MA, Tilak KS, Swyer PR: A controlled trial of assisted ventilation using an oro-nasal mask. *Arch Dis Child* 1970;45:453–459.

- 20 Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK: Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. *N Engl J Med* 1971;284:1333-1340.
- 21 Kattwinkel J, Fleming D, Cha CC, Fanaroff AA, Klaus MH: A device for administration of continuous positive airway pressure by the nasal route. *Pediatrics* 1973;52:131-134.
- 22 Wung JT, Driscoll JM Jr, Epstein RA, Hyman AI: A new device for CPAP by nasal route. *Crit Care Med* 1975;3:76-78.
- 23 Drew JH: Immediate intubation at birth of the very-low-birth-weight infant. Effect on survival. *Am J Dis Child* 1982;136:207-210.
- 24 Tyson JE: Immediate care of the newborn infant; in Sinclair JC, Bracken MB (eds): *Effective Care of the Newborn Infant*. New York, Oxford University Press, 1992, p 27.
- 25 Avery ME, Mead J: Surface properties in relation to atelectasis and hyaline membrane disease. *Am J Dis Child* 1959;97:517-523.
- 26 Soll RF: Synthetic surfactant for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2000;2:CD001149.
- 27 Soll RF, Blanco F: Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev* 2001;2:CD000144.
- 28 Soll RF: Multiple versus single dose natural surfactant extract for severe neonatal respiratory distress syndrome. *Cochrane Database Syst Rev* 2000;2:CD000141.
- 29 Yost CC, Soll RF: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev* 2000;2:CD001456.
- 30 Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, Epstein MF, Fitzhardinge PM, Hansen CB, Hansen TN, et al: Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987;79:26-30.
- 31 Van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M, Susser M, Paneth N, Leviton A: Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. *Pediatrics* 2000;105:1194-1201.
- 32 de Klerk AM, de Klerk RK: Nasal continuous positive airway pressure and outcomes of preterm infants. *J Paediatr Child Health* 2001;37:161-167.
- 33 Gittermann MK, Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC: Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. *Eur J Pediatr* 1997;156:384-388.
- 34 Meyer M, Mildenhall L, Wong M: Outcomes for infants weighing less than 1,000 grams cared for with a nasal continuous positive airway pressure-based strategy. *J Paediatr Child Health* 2004;40:38-41.
- 35 Stevens TP, Blennow M, Soll RF: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev* 2004;3:CD003063.
- 36 Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrom K, Jacobsen T: Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. *N Engl J Med* 1994;331:1051-1055.
- 37 Verder H, Albertsen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, Agertoft L, Djernes B, Nathan E, Reinholt J: Nasal continuous positive airways pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics* 1999;103:e24.
- 38 Reininger A, Khalak R, Kendig JW, Ryan RM, Stevens TP, Reubens L, D'Angio CT: Surfactant administration by transient intubation in infants 29 to 35 weeks' gestation with respiratory distress syndrome decreases the likelihood of later mechanical ventilation: a randomized controlled trial. *J Perinatol* 2005;25:703-708.
- 39 Falck AJ, Escobedo MB, Baillargeon JG, Villard LG, Gunkel JH: Proficiency of pediatric residents in performing neonatal endotracheal intubation. *Pediatrics* 2003;112:1242-1247.
- 40 Lane B, Finer N, Rich W: Duration of intubation attempts during neonatal resuscitation. *J Pediatr* 2004;145:67-70.
- 41 Leone TA, Rich W, Finer NN: Neonatal intubation: success of pediatric trainees. *J Pediatr* 2005;146:638-641.
- 42 O'Donnell CPF, Kamlin COF, Davis PG, Morley CJ: Endotracheal intubation attempts during neonatal resuscitation: success rates, duration, and adverse effects. *Pediatrics* 2006;117:e16-e21.
- 43 Kelly MA, Finer NN: Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. *J Pediatr* 1984;105:303-309.
- 44 Morley CJ, Davis PG, Doyle LW, Brion L, Hascoet J-M, Carlin JB: Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med* 2008;358:700-708.
- 45 Sandri F, Plavka R, Simeoni U; the CURPAP Advisory Board: The CURPAP study: an international randomized controlled trial to evaluate the efficacy of combining prophylactic surfactant and early nasal continuous positive airway pressure in very preterm infants. *Neonatology* 2008;94:60-62.
- 46 O'Donnell CPF, Kamlin COF, Davis PG, Carlin JB, Morley CJ: Interobserver variability of the five-minute Apgar score. *J Pediatr* 2006;149:486-489.
- 47 O'Donnell CPF, Kamlin COF, Davis PG, Carlin JB, Morley CJ: Clinical assessment of infant colour at delivery. *Arch Dis Child Fetal Neonatal Ed* 2007;92:F465-F467.
- 48 Kamlin COF, O'Donnell CPF, Davis PG, Morley CJ: Accuracy of clinical assessment of infant heart rate in the delivery room. *Resuscitation* 2006;71:319-321.
- 49 Ammari A, Suri M, Milisavljevic V, Sahni R, Bateman D, Sanocka U, Ruzal-Shapiro C, Wung JT, Polin RA: Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr* 2005;147:341-347.
- 50 Lindner W, Hogel J, Pohlandt F: Sustained pressure-controlled inflation or intermittent mandatory ventilation in preterm infants in the delivery room? A randomized, controlled trial on initial respiratory support via nasopharyngeal tube. *Acta Paediatr* 2005;94:303-309.
- 51 Horbar JD, Carpenter JH, Buzas J, Soll RF, Suresh G, Bracken MB, Leviton LC, Plsek PE, Sinclair JC, Vermont Oxford Network: Timing of initial surfactant treatment for infants 23 to 29 weeks' gestation: is routine practice evidence based? *Pediatrics* 2004;113:1593-1602.
- 52 Horbar JD, Carpenter JH, Buzas J, Soll RF, Suresh G, Bracken MB, Leviton LC, Plsek PE, Sinclair JC: Collaborative quality improvement to promote evidence based surfactant for preterm infants: a cluster randomised trial. *BMJ* 2004;329:1004-1007.
- 53 Vermont Oxford Neonatal Network: Delivery room management trial. Vermont Oxford Network 2008. <http://www.vtoxford.org/home.aspx?p=research/drm/index.htm>.
- 54 Finer NN, Carlo WA, Duara S, Donovan EF, Fanaroff AA: Delivery room continuous positive airways pressure: practice and feasibility: in reply. *Pediatrics* 2005;115:198.
- 55 Herting E: The AMV (avoiding mechanical ventilation) trial (personal communication). <http://www.controlled-trials.com/ISRCTN05025922/>.
- 56 Rabe H, Reynolds G, Diaz-Rosello J: A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. *Neonatology* 2008;93:138-144.
- 57 Saugstad OD, Ramji S, Vento M: Resuscitation of depressed newborn infants with ambient air or pure oxygen: a meta-analysis. *Biol Neonate* 2005;87:27-34.
- 58 Saugstad OD: Optimal oxygenation at birth and in the neonatal period. *Neonatology* 2007;91:319-322.