Better Neonatal Outcomes: Oxygen, Surfactant and Drug Delivery

The 28th International Workshop on Surfactant Replacement took place in Helsinki, the beautiful capital city of Finland, from May 31 to June 1, 2013. The theme for the workshop was how clinicians can continue to improve neonatal outcomes by applying the results of evidence-based research to everyday management of ill and preterm infants. In the past decade, survival rates of very preterm babies have not increased significantly but the focus of attention has been to improve the quality of life of survivors. There have been many randomized trials evaluating different management practices in the delivery room and in the early life of very preterm infants. In addition, basic and translational research is aimed at a better understanding of the pathogenesis leading to the discovery of new therapies. The speakers at the workshop discussed recent discoveries that are likely to influence the outcome of high-risk infants. The workshop comprised the 5th Bengt Robertson Memorial Lecture, five other excellent overview presentations by world-renowned experts, sixteen orally presented free communications and twelve poster presentations. The workshop was attended by over 300 participants from about 50 countries, including Germany, Sweden, Finland, Norway, Denmark, China, the Netherlands, Turkey, Russia, Greece, UK, USA, Brazil, Slovenia, Slovakia, Switzerland, Canada and Poland.

The 5th Bengt Robertson Memorial Lecture was given by Mikko Hallman from Oulu, Finland, someone who has been researching surfactant from both a scientific and

clinical point of view for about 40 years [1]. Indeed, the first randomized trial of surfactant replacement for severe respiratory distress syndrome (RDS) using natural surfactant from human amniotic fluid was reported by Hallman et al. [2] in 1985. Surfactant replacement and concomitant treatment practices have virtually eliminated fatal respiratory failure soon after preterm birth. In addition, RDS can no longer be accurately defined as very early treatment practices have transformed the disorder to a milder form. Of course, this situation would not have been possible without the pioneering research of Bengt Robertson [3] and his colleague Goran Enhörning in the 1970s. The 5th Bengt Robertson Memorial Lecture was entitled 'The Surfactant System Protects Both Fetus and Newborn' and Mikko Hallman discussed the important role of surfactant in preventing pulmonary infection as distinct from its effect on reducing lung surface tension. Surfactant proteins A and D (SP-A, SP-D) are not present in commercial surfactant preparations as they are not essential in the treatment of RDS. Surfactant components and molecules interacting with the complex undertake versatile roles in host defense [4]. The surfactant system in human pregnancy may be induced in early gestation and secreted in the future airways and amniotic fluid, but despite this and treatment with antenatal steroids, surfactant deficiency at birth is relatively common. Besides surface tension and mechanical shear-reducing functions, surfactant reduces inflammatory responses that threaten

lung development, perinatal transition and postnatal growth [5].

Tore Curstedt from Stockholm who, along with the late Bengt Robertson [3], first formulated the porcine surfactant Curosurf (so named from the first letters of their surnames), updated the workshop attendees on progress with new generation synthetic surfactants. Tore Curstedt told the audience that synthetic surfactants had moved on since 2006 when the question ‘new synthetic surfactant – how and when?’ was posed [6]. Surfactant proteins B and C (SP-B and SP-C) have different actions in vivo [7], and it is clear that synthetic surfactant based on analogs of the two hydrophobic proteins SP-B and SP-C is superior to single-peptide surfactants in the ventilated preterm rabbit model [8]. Another often ignored issue is the lipid concentration of synthetic surfactant. Clinical trials are likely to follow, aimed at determining the precise role for new synthetic surfactants in clinical practice. There may be an expanded role for surfactant therapy in the treatment of respiratory disorders characterized by surfactant inhibition or inactivation rather than a primary deficiency. Optimal synthetic surfactants containing two peptides combined with a more complex phospholipid composition seem to be ideal to replace natural surfactants in the near future. The design of new generation synthetic surfactants may be important for both their effectiveness and suitability for noninvasive administration.

Delivery room management of very preterm infants and indeed term infants may be critical for their intact survival. Roger Soll from Burlington, Vermont, the chair of the Neonatal Review Group of the Cochrane Collaboration, reviewed evidence-based practices in the stabilization of immature infants. His talk updated the recommendations given in a previous presentation to an earlier workshop [9]. It is stressed that most preterm babies do not need resuscitation (in the true sense of the word) but merely help with transition or stabilization. Rather than immediate endotracheal intubation, increasingly used strategies of initial respiratory support of preterm infants comprise the use of continuous positive airway pressure (CPAP) in the delivery room and early administration of surfactant if needed, followed by immediate extubation to CPAP [10]. The latter is the INSURE method comprising INTubation, SURfactant and Extubation, which has been used for many years in Scandinavia before spreading to the rest of Europe and finally to the USA. Less invasive methods of surfactant administration were topics discussed at our last workshop in Lisbon [11–13] and these have been endorsed in the updated European Guidelines for the Management of RDS published in this issue of

Neonatology [14]. Another important issue is ensuring that very preterm births occur in centers with adequate capacity and that the personnel involved have experience and training in the stabilization of such babies.

The next review was on drug delivery using the airways and it was presented with great clarity by Eric Shinwell from Jerusalem, Israel. Apart from surfactant many different drugs have been administered intratracheally to newborn infants; the list includes inhaled steroids [15], steroids given with surfactant, pulmonary vasodilators, bronchodilators, adrenaline (or epinephrine) and the mucolytic drug DNase. The indications for administering airway medications include prevention and treatment of bronchopulmonary dysplasia, pulmonary hypertension, persistent atelectasis, transient tachypnea of the newborn [16] and upper airway edema. Eric Shinwell concluded that, although airway medications are an attractive route of intervention for a variety of conditions in sick neonates, most of the potential indications need more thorough investigation.

Keith Barrington from Montreal, Canada, reviewed the still controversial area of hemodynamic management of ill and preterm infants. Systematic research on the cardiovascular system, which is intimately linked with the respiratory system in neonatal transition, has been lacking until recently. There is no agreement on a definition of hypotension in very preterm infants and there are still doubts about whether treatment improves the outcome of babies with low blood pressure [17]. However, there are now ongoing studies such as the HIP Trial which will help refine our management of hypotension in extremely low birth weight infants [18]. Cardiac output, the distribution of vascular volumes and the microcirculation at both pulmonary and systemic levels provide the basis and critical components of oxygen uptake by vital organs. Increasing the blood volume of a depressed or very preterm baby by delayed cord clamping is beneficial although there is no agreement on the precise technique to be used [13, 19, 20]. There is a need for further research and analysis of randomized trials using individualized meta-analyses.

The final speaker tackled another controversial problem, namely, that of setting targets for oxygen therapy of very preterm infants [21]. Ben Stenson from Edinburgh, reminded us that although the knowledge that extreme hypoxia or hyperoxia is harmful, the middle ground in between remains uncertain for both preterm and term babies [22]. There is growing evidence that targeting oxygen saturations below 90% is associated with increased mortality in extremely low birth weight infants [20] al-

though severe retinopathy of prematurity may be decreased. One of the problems encountered in the BOOST II trials was that the characteristics of the original algorithm for the Masimo SET pulse oximeter reduced the frequency of saturations of 87–90% and increased the frequency of higher values [21]. With the new algorithm this problem was solved and the improved survival with higher oxygen saturation targets was revealed [20]. At present, oxygen saturation targets for extremely preterm infants should not go below 90% [13, 19, 23].

The postconference workshop comprised a number of interesting discussions. Sture Andersson from Helsinki and Mats Blennow from Stockholm debated the benefits and risks of regionalization of perinatal and neonatal care. They agreed that proper regionalization is a cost-effective approach that improves the survival of high-risk infants. Dominique Haumont from Brussels discussed online registration of nosocomial infections in the NICU. Roger Soll reviewed trials of red blood cell transfusion practices and erythropoietin therapy. Whilst erythropoietin is potentially an antioxidant, its use has been associated with an increase in retinopathy of prematurity [24], as has blood transfusion, in keeping with the knowledge that stored red blood cells have oxidant properties. Jatinder Bhatia from Augusta addressed the important problem of fetal and postnatal growth restriction. He underscored the evidence indicating a remarkable association between quantity and quality of nutrient intake after birth and neurological outcome. Finally, the new European guidelines on the management of RDS [14] were present-

ed by David Sweet from Belfast. These updated guidelines were developed by a consensus group of leading neonatologists from all over Europe who based their recommendations on evidence from randomized controlled trials and meta-analyses. The guidelines are published in this issue of *Neonatology* and will be updated again in 3 years when more information from ongoing trials should become available.

The current issue of *Neonatology* contains the studies and abstracts from the workshop and we would like to honor and remember Bengt Robertson [3] who founded this series of workshops in 1986 and was the architect of our understanding of neonatal RDS and its treatment with surfactant.

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Tore Curstedt, Stockholm
Henry L. Halliday, Belfast
Ola D. Saugstad, Oslo
Christian P. Speer, Würzburg

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