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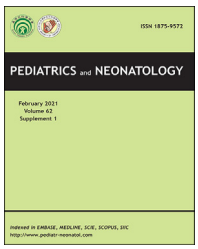

Mini Review

Respiratory distress syndrome in preterm neonates in the era of precision medicine: A modern critical care-based approach

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Respiratory distress syndrome (RDS) was recognized to be caused by primary surfactant deficiency almost 70 years ago and continuous positive airway pressure was introduced approximately 50 years ago. Since then, there have been many developments in neonatology; we know many things but others are still controversial. The more we know, the more questions arise. However, this review aims to indicate what is more needed to understand and how should be the modern approach to RDS in the era of precision medicine. The review is divided between new concepts and new tools. We will explain the interaction between steroids, CPAP and surfactant, as well as the surfactant catabolism and the diagnosis of NARDS; lung ultrasound and new tools to optimize CPAP will also be covered. How these concepts are integrated in the author's personal experience is also illustrated.

1. A bit of history

Respiratory distress syndrome (RDS) is a common reason for neonatal intensive care unit (NICU) admission. RDS was originally indicated as idiopathic respiratory distress syndrome (iRDS) or "hyaline membrane disease" (HMD), based on the histological presence of alveolar layers of fibrin and necrotic cells originally described in the *Lancet* in 1953.[1] It was finally re-named RDS after it was shown to be caused by primary surfactant deficiency.[2]

The obvious consequence was the discovery and availability of surfactant replacement as a causal therapy. The

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purpose of this review is to focus on what happened next and what the modern approach to RDS in 2020 should be. Do we know everything about RDS in preterm neonates? Did we obtain significant improvements and are there others yet to be achieved? The answers are no and yes, respectively. For instance, we do not know if more than 200 mg/kg surfactant can be given to safely and efficaciously to treat RDS,[3] but we do know that poractant-alpha (a porcine surfactant) is superior to bovine surfactants[4] and that all bovine surfactants are clinically equivalent, irrespective of their composition and preparation method.[5]

There are many ongoing novelties about RDS in preterm neonates and I will divide these into conceptual and technical ones.

2. New concepts

2.1. Steroids, CPAP and surfactant interaction

After years of general "surfactant prophylaxis", the European and American guidelines, in 2013 and 2014, respectively, recommended surfactant replacement only when continuous positive airway pressure (CPAP) failed.[6,7] This change followed a number of randomized clinical trials demonstrating the superiority of early CPAP on universal mechanical ventilation for preterm neonates in terms of mortality and/or bronchopulmonary dysplasia (BPD).[8] An early, uninterrupted and optimally delivered CPAP may spare surfactant replacement in a significant proportion of cases, even in extremely preterm infants and this also is our everyday experience. This has solid pathobiological background since preterm neonates need 4/5 days to produce endogenous surfactant[9] and, during this period, CPAP may open up the lung and keep it open. Thus, surfactant replacement became a second-line, rescue therapy only reserved for those failing CPAP, to be administered as quickly as possible, since surfactant efficacy is highest in the first 2/3 h of life.[10] This strategy has ensured better clinical outcomes and reduced invasiveness, as well as costs.[11] The picture has become even clearer because prenatal steroids have also been introduced as fetal therapy: they boost surfactant production and this has reduced the incidence of RDS and need for surfactant replacement, while improving clinical outcomes.[12]

Invasive mechanical ventilation is rarely needed in the triple therapy "prenatal steroids-CPAP-early rescue surfactant" and mechanical ventilation is associated with negative clinical outcomes.[13] Irrespective of the technique for surfactant administration, this combined triple therapy is highly efficacious in RDS and even extremely preterm neonates very often can be managed without invasive ventilation, and sometimes without surfactant. Invasive ventilation may still be needed when RDS is not the only or main cause for respiratory failure, that is when other superimposed disorders determine a more severe clinical picture. This is the case in pulmonary hypoplasia or neonatal acute respiratory distress syndrome (NARDS), whose diagnosis and management may not be easy (see below).

The modern approach to RDS in preterm neonates consists of the interactive therapy comprising universal prenatal steroids prophylaxis, early CPAP application and surfactant replacement, as soon as possible, but only when CPAP fails. The crucial issue here is that it is unclear how to reliably recognize babies who are going to fail CPAP. In other words, for each baby, we still have to answer the question: *"can we stay and play with CPAP or should we give surfactant?"* This is a very important question and cannot be answered by choosing a particular surfactant administration technique, but only by understanding the physiopathological and biological situation of each patient. Thus, surfactant should be given in a much more guided and personalized way, which is nowadays possible (see below).[14]

2.2. Surfactant catabolism and the diagnosis of NARDS

For many years, surfactant deficiency was thought to be the cause of almost all respiratory failures in preterm neonates. This was caused by the dichotomy between RDS and ARDS when, in the 60s, the "*A*" in the acronym meant "Adult". In 1967 the original description of ARDS reported clinical and histological characteristics very similar to RDS ("*dyspnea, tachypnoea, cyanosis resistant to oxygen therapy, loss of lung compliance and diffuse alveolar infiltration*", and "*areas of atelectasis, alveolar oedema and hemorrhage*" at necropsy).[15] Thus, the only way to distinguish the two disorders was patient age.

In reality, RDS and ARDS have similar clinical features but differ from a pathophysiological point of view, since RDS is caused by primary surfactant deficiency combined with structural immaturity of the lung, while ARDS occurs in patients who have functional surfactant and developmentally normal lungs prior to ARDS onset.

Fortunately, our knowledge on ARDS significantly evolved and the "*A*" now stands for "acute", recognizing that the clinical manifestations of ARDS are not limited to any specific age groups. In fact, from a biological point of view, ARDS is characterized by an increased surfactant catabolism leading to a qualitative and quantitative surfactant injury, lung tissue inflammation and endothelial/epithelial damage.[16] These mechanisms have been demonstrated in adults,[17,18] children[19,20] and also neonates,[21,22] and, therefore, it is not surprising that specific definitions for the diagnosis of ARDS in adults,[23] children (Pediatric ARDS, PARDS)[24] and neonates (NARDS)[25] have become available.

As ARDS may occur at any age, this introduces significant complexity and leads us to understand that the respiratory failure in preterm neonates may be much more difficult than has been thought. In fact, for instance, a 25 weeker in the first days of life, in addition to primary surfactant deficiency, may have early-onset sepsis and this may trigger NARDS mechanisms. In this case the physiopathology will be more complex and the clinical picture potentially much more severe. Surfactant replacement will be less efficacious, as exogenous surfactant will also be damaged by NARDS mechanisms and CPAP will more likely leave its place to invasive ventilation. From a molecular point of view, a main responsible for surfactant injury during ARDS is

secretory phospholipase A2 (sPLA2), an enzyme produced by alveolar macrophages, which catabolizes surfactant phospholipids and regulates the first step of the inflammatory cascade.[26] From a clinical point of view, the definition of NARDS ('Montreux definition') provides criteria to diagnose the syndrome and distinguish it from pure RDS by the complete, sustained and prompt response to surfactant, or lung recruitment, or both. This response is absent when a lot of inflammation and surfactant catabolism are present, that is, when NARDS is the primary cause for respiratory failure.

Distinguishing RDS and NARDS is not a purely academic exercise; it allows us to understand the severity of the respiratory failure and personalize the respiratory support, while it will allow new therapies in the future. In fact, possible new therapies are summarized by the following open question: *"Do we need to increase the surfactant dose, or do we need some therapeutics to protect surfactant in neonates with NARDS?"* When the lung is challenged with extensive inflammation and sPLA2, we ideally would like to use a higher surfactant dose, or more resistant surfactants or molecules able to increase its efficiency and protect it from catabolism. These strategies Budesonide, sPLA2 inhibitors and surfactant-protein D are some examples which are being trialed in clinical or preclinical research.[27–29]

3. New tools

3.1. Lung ultrasound

RDS severity was originally classified by conventional chest X-rays and, without doubt, some neonatologists still demand a chest film as a sort of "confirmatory" diagnostic tool. In the daily practice, the need to act quickly[8] and its unreliability[30,31] have greatly reduced the use of conventional radiology in the management of RDS. In fact, CPAP should be started very early and no radiological criteria to guide surfactant replacement have reached accuracy and consensus; thus chest X-rays have no place in the current guidelines[32] and in the modern approach to RDS in 2020.

While conventional chest film is not an useful imaging tool in the management of RDS, clinicians remain in need of a quick, repeatable, reliable, highly informative and easy-to-use technique. Lung ultrasound fulfils all these characteristics and is also radiation-free.[33] It has entered the clinical management of ARDS in adults[34] and has been included in adult medicine guidelines.[35] With a long delay, lung ultrasound finally started to be diffused also in neonatology and its usefulness to diagnose RDS is currently well known; lung ultrasound accurately distinguishes RDS from other types of respiratory failure,[36,37] but it is also able to predict CPAP failure[38,39] and guide surfactant replacement.[40] This policy has been called ESTHER (Echography-guided Surfactant THERapy) and it is based on a semiquantitative lung ultrasound score that has proven its reliability in multiple independent studies.[41,42]

Fig. 1 illustrates the time-line for the NICU admission of extremely preterm inborn neonates (the so-called "golden hour") according to the protocol enforced at the Paris Saclay University Hospitals, *"A.Béclère"* medical center. The protocol aims to reduce unnecessary manipulations and acts, to leave as much time as possible for stabilization and lung ultrasound in order to apply ESTHER and decide if the baby can stay on CPAP or if surfactant is needed within the 3rd hour of life.

Therefore, lung ultrasound allows us to answer the question: *"Can we stay and play in CPAP or should we give surfactant?"*. It represent the link between CPAP and surfactant as it may be used to predict CPAP failure, personalize surfactant treatment[14] and eventually also evaluate the course of respiratory failure after surfactant replacement. In fact, lung ultrasound scores have been used to evaluate lung aeration after surfactant therapy to predict BPD in infants,[43] and also to titrate mechanical ventilation in adult and infants.[44,45] Thus, they might also be useful in complicated cases where RDS and NARDS are superimposed and invasive ventilation is needed.

Lung ultrasound is not the only promising tool to obtain informative imaging of RDS, as electrical impedance tomography,[46] segmentography[47] and diaphragm ultrasound[48] might provide useful insight into RDS physiopathology. However, these tools are far less developed than lung ultrasound, which already has its place in international evidence-based guidelines for the point-of-care ultrasound in pediatric and neonatal critical care.[49] The remaining open questions in this field are: *"How to improve reliability, which is already very good, of lung ultrasound to predict surfactant need?"* and *"how to increase the diffusion of the technique?"* Lung ultrasound has a steep learning curve[50] and it has been easily introduced in developing countries,[51] but we do not have yet enough formal data about its training, while these are available in adult critical care.

3.2. Optimization of CPAP therapy

Although lung ultrasound may quickly diagnose RDS in the first hours of life and indicate who is going to receive surfactant, CPAP remains the mainstem therapy to be provided. Nasal CPAP was introduced approximately 50 years ago[52] and we now know many important details to optimize its efficacy: this is important if we really want to exploit its potential, both as stand-alone intervention and as interactive therapy combined with antenatal steroids and surfactant.

CPAP is better transmitted if delivered through nasal mask in the first days of life and this seems also to reduce the risk of local skin injury.[53,54] However, we have to acknowledge that nasal CPAP unavoidably has relevant leaks up to around 40% with mouth opening,[55] irrespective of the nasal interface used[56–59] and the same applies for more complex techniques of non-invasive respiratory failure.[60] As the optimal CPAP level to be provided in preterm neonates with RDS is not known, we also ignore if active mouth closure may be beneficial.

There are several ways to generate CPAP, but we lack definite data to identify the best. Clinical data are conflicting on this point and outcomes are not clearly changed using one CPAP system or another. However, from a mechanical point of view, CPAP generated with variable flow

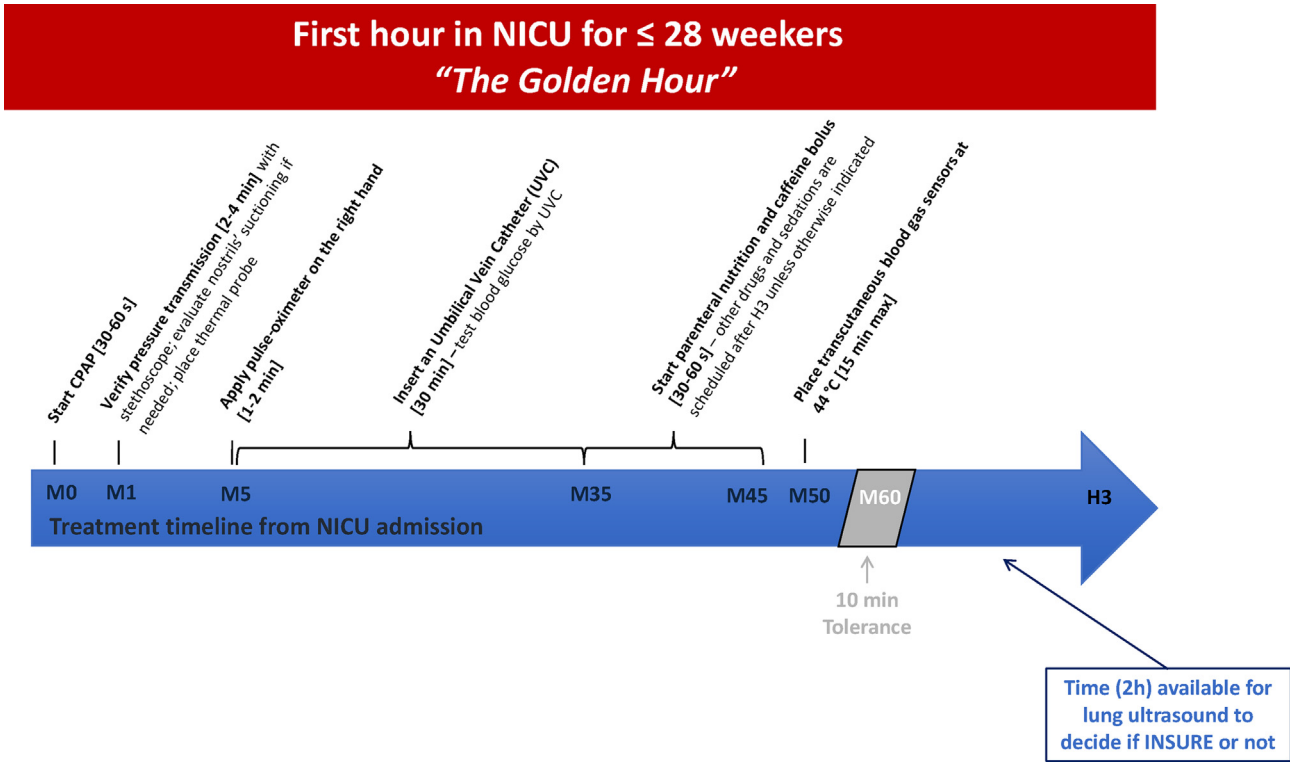

Figure 1 The golden hour of an extremely preterm inborn neonate (i.e.: the first hour in the NICU). This graph depicts the procedure in use at the Paris Saclay University Hospitals, "*A.Béclère*" medical center. The protocol aims to reduce unnecessary manipulations and acts, and to leave as much time as possible for the stabilization and lung ultrasound in order to decide if the baby can stay on CPAP or if surfactant is needed within the 3rd hour of life. Numbers in squared parentheses indicate the estimate time for the act. Medical and non-medical personnel is cyclically trained for this protocol (and its timeliness), which is reproduced in the high-fidelity simulation room. **Abbreviations**: CPAP: continuous positive airway pressure; INSURE: intubation-surfactant-extubation procedure; NICU: neonatal intensive care unit; M: minute. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

system using the Venturi-Coanda effect seems to be more physiologically sound and able to optimize lung mechanics in preterm neonates with RDS.[61] Conversely, bubble CPAP generated by water valve has a very low cost and ease of use and this may facilitate its diffusion also in low income settings.[62]

We do not know the best pressure level to be chosen in the early phase of RDS and this remains a major problem. However, relatively high CPAP levels (7/9 cmH_2O) have been able to reduce extubation failure in preterm infants[63] and they are often used at least in some NICU protocols.[7] Based on these experiences, the European guidelines suggest at least 6 cmH_2O of CPAP.[32] Unfortunately, the optimal CPAP level is to reduce work of breathing in the early phase of RDS in preterm neonates is not yet known, while this has been discovered in bigger infants,[64] essentially because preterm neonates are too small for easy and reliable measurements of esophageal pressure and advanced lung mechanics studies. However, miniaturized tools may become available and the neurally adjusted ventilator assist (NAVA) probes are already marketed. These, besides providing NAVA ventilation, have also been used to monitor electrical activity of the diaphragm (EAdi) in neonates, and EAdi resulted strongly correlated with esophageal pressure and related work of breathing estimation.[64]

Finally, when weaning smaller babies from CPAP, gradual reduction rather than sudden cessation of pressure results in greater likelihood of weaning on the first attempt.[65] This is physiologically sound and consistent with the data accumulated in adult patients.

3.3. Surfactant administration techniques

We cannot claim to have developed relevant new tools to significantly improve surfactant administration for RDS, although surfactant administration techniques have been the object of extensive research in the last years. Ideally a nebulized surfactant would be totally non-invasive as it would spare sedation and intubation and could be administered easily. However, this is not clinically available. The so-called "less invasive surfactant administration techniques" have spread, but they cannot provide the same advantages, as they require sedation and intubation.[55] In absence of sedation these techniques may be ethically questionable.[55] Furthermore, they have significant problems as CPAP is not transmitted during these procedures, and the surfactant distribution may not be as effective.[56,66] Moreover, the theoretical advantages of these techniques are unclear, since trials have been significantly biased and

they lack a clear background to be superior to the actual intubation-surfactant-extubation (INSURE) technique.[55]

Conversely, supraglottic devices are being developed and investigated in preliminary trials, although with delay compared to their use in adult and pediatric anesthesia. The use of these devices can finally be a significant improvement, since they can be placed easily and without any sedation.[55] They can also be used by allied healthcare professionals and this can facilitate the use of surfactant. Currently, evidence about these tools is scarce but there is a strong pathobiological background and they are likely to be more deeply investigated in the near future.[67]

4. Final suggestions for the modern approach

My personal belief is that the modern approach to RDS should be personalized, based on physiopathology and critical care perspective, which can only be built by cross-disciplinary awareness. This is an example of precision medicine concepts, which is much needed in neonatology. Complex medical problems almost never have easy solutions and, in the era of precision medicine, we should critically focus on the aforementioned advances.

Declaration of competing interest

Prof.De Luca has received research and educational grants from Chiesi Pharmaceuticals spa and ABBVIE Inc. He served as consultant and lecturer for Airway Therapeutics, Chiesi Pharmaceuticals spa and ABBVIE Inc. Finally, he has been member of advisory boards for Chiesi Pharmaceuticals spa and ABBVIE Inc. These companies produce surfactants or surfactant proteins but they had no role in design, preparation, review, approval of the manuscript or decision to submit it for publication. The declared conflicts are all unrelated to the present work.

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