

# The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity

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Acute respiratory distress syndrome (ARDS) is undefined in neonates, despite the long-standing existing formal recognition of ARDS syndrome in later life. We describe the Neonatal ARDS Project: an international, collaborative, multicentre, and multidisciplinary project which aimed to produce an ARDS consensus definition for neonates that is applicable from the perinatal period. The definition was created through discussions between five expert members of the European Society for Paediatric and Neonatal Intensive Care; four experts of the European Society for Paediatric Research; two independent experts from the USA and two from Australia. This Position Paper provides the first consensus definition for neonatal ARDS (called the Montreux definition). We also provide expert consensus that mechanisms causing ARDS in adults and older children—namely complex surfactant dysfunction, lung tissue inflammation, loss of lung volume, increased shunt, and diffuse alveolar damage—are also present in several critical neonatal respiratory disorders.

## Introduction

Acute respiratory distress syndrome (ARDS) is undefined in neonates, despite the longstanding recognition of ARDS in later life. We describe the Neonatal ARDS Project: an international, collaborative, multicentre, and multidisciplinary project which aimed to produce an ARDS consensus definition for neonates that is applicable from the perinatal period. This project is an initiative endorsed by the European Society for Pediatric and Neonatal Intensive Care (ESPNIC) and the European Society for Pediatric Research (ESPR). The Steering Committee of the Neonatal ARDS Project first reviewed the literature on the biological, pathophysiological, and histological features of ARDS in neonates compared with other age groups, and on the current definitions of ARDS in older children and adults. The consensus definition was then developed from this literature analysis. This paper also presents the rationale for issuing a specific definition of ARDS in neonates.

## Age and evolution of the ARDS definition

ARDS was originally reported in 12 patients (including an 11-year-old) by Ashbaugh and colleagues<sup>1</sup> in *The Lancet* in 1967. They characterised ARDS as “dyspnoea, tachypnoea, cyanosis resistant to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration” and “areas of atelectasis, alveolar oedema, and haemorrhage” at necropsy. The clinical and histological similarities with respiratory distress syndrome (RDS) in neonates due to primary surfactant deficiency<sup>2,3</sup> were recognised early. Indeed, the “A” in the ARDS acronym stood initially for adult to delineate the two entities. Although both RDS and ARDS shared similar clinical features, differentiation of the two syndromes was justified on the basis of pathophysiological and aetiological differences. Arguably this differentiation has limited the awareness of ARDS in neonatal medicine for a long time.

The definition of ARDS has evolved substantially since 1967 because of our increasing knowledge of

surfactant biology and ARDS physiopathology. ARDS is now more accurately termed acute respiratory distress syndrome, which recognises that the clinical manifestations of ARDS are not limited to specific age groups. Treatment with positive end expiratory pressure was found to be effective<sup>4</sup> and decreased respiratory system compliance was shown.<sup>5</sup> In parallel, ARDS was recognised as a diffuse, rather than localised, process within the lung tissue. This important concept gave rise to

### Key messages

- Acute respiratory distress syndrome (ARDS) exists in neonates and might occur independently of gestational age, a hypothesis which is supported by the similar biological and pathophysiological features of ARDS and several critical respiratory conditions that are typical in neonates.
- Neonatal ARDS, which is similar to ARDS in older children and adults, is characterised by extensive lung inflammation and surfactant catabolism leading to lung dysfunction. These mechanisms can occur simultaneously with other mechanisms typical of neonatal age (ie, quantitative surfactant deficiency and lack of alveolarisation).
- A specific definition for neonatal ARDS (the Montreux definition) has been issued by expert consensus after literature revision by experts in neonatal, paediatric, and adult respiratory critical care and with the endorsement of the European Society of Neonatal Intensive Care and the European Society for Paediatric Research.
- The Montreux definition for neonatal ARDS closely resembles the definition of ARDS in patients of other ages, but the peculiarities of newborn infants and the characteristics of neonatal critical care are also considered.
- The Montreux definition might be used for clinical, epidemiological, and research purposes. A multicentre, international, prospective, web-based cohort study has been launched to describe the clinical course and outcome of neonates with ARDS.

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a radiological definition of ARDS consisting of bilateral irregular alveolar infiltrates with the involvement of several lung fields (the characteristic white lung).<sup>6</sup> A threshold of pulmonary capillary pressure was then included to allow the distinction of ARDS from congestive heart failure.<sup>6</sup> The concept that ARDS might be caused by a plurality of primary pulmonary or secondary non-pulmonary conditions with several risk factors, was introduced in 1988.<sup>7</sup> The resulting lung injury score created by Murray and colleagues<sup>7</sup> was modified by Newth and colleagues<sup>8</sup> almost a decade later and a paediatric version was proposed. The externally validated paediatric lung injury score essentially consists of Murray and colleagues<sup>7</sup> score using different positive end expiratory pressure thresholds and with the compliance indexed to the patient's weight.<sup>9,10</sup>

The definition of ARDS as a pathological and clinical entity has evolved via expert consensus over more than 20 years. The 1994 American–European Consensus Conference definition has been used widely for research and clinical care.<sup>11</sup> However, the American–European Consensus Conference definition is often criticised due to: the lack of an acute timeframe; the imprecise assessment of oxygenation impairment; the absence of a specific list of risk factors; and the need for an invasive pulmonary capillary pressure measurement. The recent Berlin definition<sup>12,13</sup> addressed these limitations and additionally postulated three classes of clinical severity. The Berlin definition was validated in a large population of patients enrolled in ARDS trials and hospital databases and is more accurate than the American–European Consensus Conference definition in predicting mortality or ventilator-free days.<sup>12,13</sup> Although respiratory system compliance was measured in patients with severe ARDS, its use did not improve mortality prediction and hence was excluded from the final Berlin definition.<sup>12</sup>

ESPNIC conducted the first international multicentre study to validate the Berlin definition in infants (older than one month) and toddlers with paediatric ARDS.<sup>14</sup> Other paediatric validations of the Berlin definition have followed.<sup>15,16</sup> Subsequently, the Paediatric Acute Lung Injury Consensus Conference (PALICC), a group of international paediatric intensivists, issued the first specific definition for paediatric ARDS.<sup>17</sup> The PALICC definition represents a major advancement in defining ARDS, but does not specifically address the peculiarities of neonatal age or include the manifestations of ARDS in the perinatal period.

The PALICC and Berlin definitions share important characteristics but relevant differences also exist.<sup>12,13,17</sup> PALICC accepts the use of pulse oximetry-based criteria when partial pressure of arterial oxygen (PaO<sub>2</sub>) is unavailable; PALICC uses oxygenation index and oxygen saturation index instead of the PaO<sub>2</sub>-to-inspired oxygen fraction (FiO<sub>2</sub>) ratio and allows the inclusion of children with pre-existing chronic lung disease or cyanotic congenital heart disease. When evaluating the application

of different ARDS definitions, using PALICC criteria increases the number of patients diagnosed with paediatric ARDS and lowers the overall mortality rate.<sup>18</sup> However, severe paediatric ARDS is associated with high mortality, particularly if the disorder is present 24 h after the initial diagnosis.<sup>18</sup>

### Why do we need a definition of neonatal ARDS?

The first month of life (ie, the neonatal period) is a unique life-stage characterised by a high risk of mortality.<sup>19</sup> The American Academy of Pediatrics recommends that causes of mortality would be specifically defined for the first month of life and include perinatal events and the degree of fetal maturation.<sup>20</sup> The PALICC definition<sup>17</sup> specifically excludes causes of acute hypoxaemia that are unique to the perinatal period. Primary RDS related to prematurity is clearly different from paediatric ARDS and should be excluded. However, no biological or clinical evidence suggest that acquired perinatal severe lung injuries, such as meconium aspiration syndrome or congenital diffuse pneumonia, differ from paediatric ARDS. Rather, strong evidence suggests that the mechanisms associated with ARDS also occur in some neonatal severe respiratory disorders.

The exclusion of neonatal disorders from the ARDS spectrum reduced cross-disciplinary awareness. In fact, neonatologists are often unfamiliar with the literature on adult and paediatric ARDS, whereas paediatric intensivists are often unaware of the occurrence of critical neonatal respiratory disorders in neonates. Failure to recognise a common ARDS spectrum and the lack of interdisciplinary knowledge transfer have reduced the links between centres, diffusion of optimal clinical care, and research possibilities in neonatal ARDS. Moreover, in some geographical areas, critically ill neonates might be cared for both in neonatal and paediatric intensive care units.<sup>21,22</sup>

Although the PALICC definition is independent of patients' age,<sup>17</sup> some aspects reduce its suitability for neonates. Neonatal critical care has specific technical features related to patient size. Some clinical tools and monitoring techniques used in the PALICC definition are uncommonly used in neonatal critical care, including cuffed tubes and the measurement of respiratory dead space or static compliance, either because these clinical tools are intractable or because neonatal ventilators do not commonly provide some techniques (eg, end-inspiratory and end-expiratory occlusion). The unpredictable physiological effects of fetal life transition, such as variable fetal haemoglobin concentration, might also influence peripheral oxyhaemoglobin saturation (SpO<sub>2</sub>), SpO<sub>2</sub>-to-FiO<sub>2</sub> ratio, and pulmonary shunts.<sup>23,24</sup> Whereas PALICC includes bilevel positive airway pressure ventilation, its use in neonatal critical care is infrequent, lacks evidence,<sup>25</sup> and is often unavailable in many neonatal ventilators. Conversely, the use of high frequency oscillatory ventilation is more common in neonatal critical

care and is corroborated by greater evidence than in older children and adult patients.<sup>26,27</sup> Furthermore, the nature and consequences of severe respiratory failure in neonates are complicated by developmental factors that can influence the prognosis and epidemiology. Neonates could have: unique triggers for respiratory failure (eg, meconium aspiration syndrome, perinatal asphyxia, necrotising enterocolitis) that might differ for ARDS and paediatric ARDS; variations in specific aspects of developmental lung biology and maturation (saccular or early alveolar stage), and the susceptibility to bronchopulmonary dysplasia, which can present different long-term consequences in neonates compared with lung injuries in older children and adult patients; and reduced local and systemic immune defences, potentially causing more severe clinical pictures.

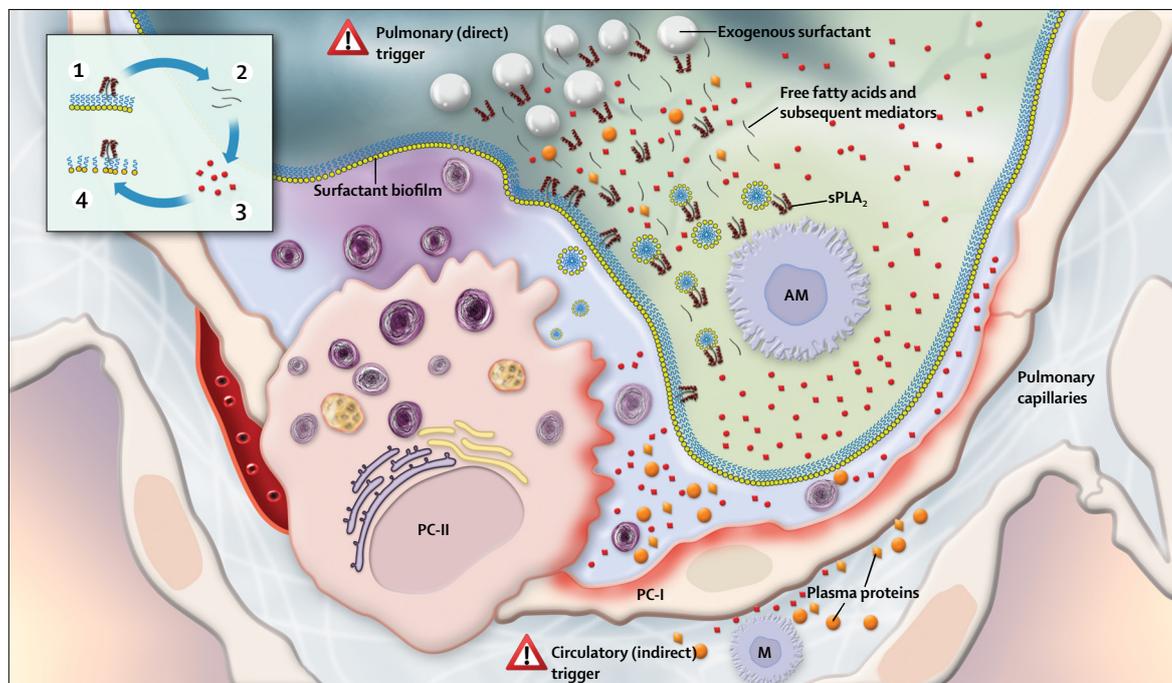
Consequently, we argue a strong case exists for a definition of ARDS specific to the first month of life. Such a definition would increase the awareness of severe respiratory failure in neonates and link existing expertise in the paediatric and adult critical care community with neonatal practices. This definition would additionally

help to predict prognoses and guide health-care professionals on which therapies to use on the basis of their suitability or risk-to-benefit ratio.<sup>12,13</sup> The neonatal ARDS definition would foster basic research, improve the understanding of neonatal ARDS epidemiology, and guide uniform care for patients with ARDS, with potential public health benefits.

### Does neonatal ARDS really exist?

From our search strategy we retrieved 32 publications that used the term neonatal ARDS: 23 clinical (mainly case series) and nine translational neonatal animal model studies (see appendix). The first use of the term neonatal ARDS in 1989 described 11 term neonates with ARDS associated with perinatal asphyxia and meconium or blood aspiration.<sup>28</sup> Faix and colleagues<sup>28</sup> concluded that “ARDS can and does occur in newborn infants. We see no reason why this syndrome could not be superimposed on some of the more classical neonatal respiratory diseases to produce an even worse clinical situation”.<sup>28</sup> All 11 infants had ARDS caused by perinatal conditions, which would have not fulfilled the PALICC definition.<sup>17</sup>

See Online for appendix



**Figure 1: Biology of a neonatal ARDS and interplay with exogenous surfactant administration**

An alveolus is depicted with surfactant secreted as lamellar bodies and forming the biofilm on the alveolar surface. Danger signs represent the ARDS triggers including direct triggers (eg, pneumonia and meconium or milk aspiration) or indirect triggers (eg, fetal inflammation, sepsis, and necrotising enterocolitis). Red squares and circles represent the different pro-inflammatory mediators, reactive oxygen species, and proteases secreted into the alveolar space and pulmonary capillaries. The effect of ARDS on cellular damage is represented by the shaded red on membranes of alveolar cells. Plasma proteins extravasating in the alveolar space might further injure the surfactant film and are represented by orange balls and squares. Secretory phospholipase A2 is secreted by alveolar macrophages and is shown with its miniaturised tridimensional structure (courtesy of M C De Rosa, Lab of Molecular Modelling, National Research Council, Rome, Italy) attached to the surfactant phospholipid layer. Free fatty acids released from surfactant phospholipid hydrolysis are represented as thin short lines. The box summarises the vicious cycle<sup>27</sup> represented by: (1) the phospholipase-driven surfactant phospholipid hydrolysis; (2) production of free fatty acids; (3) derived inflammatory mediators; (4) further injury to the surfactant. Exogenous surfactant reaching the alveolus through the airways is represented by white balls. Phospholipase A2 might also hydrolyse exogenous surfactant, producing free fatty acids, which can lead to the production of further inflammatory mediators. Plasma proteins and other inflammatory mediators also injure exogenous surfactant. A comprehensive list of pathological mechanisms and references is provided in the appendix. ARDS=acute respiratory distress syndrome. AM=alveolar macrophage. M=monocyte. PC-I=type 1 pneumocyte. PC-II=type 2 pneumocyte. sPLA2=secretory phospholipase A2. This figure is adapted from Raghavendran and colleagues<sup>41</sup>.

	ARDS	Paediatric ARDS	Neonatal ARDS				
			Sepsis	Pneumonia*	MAS	Aspiration†	Lung haemorrhage
$C_{rs}$	Large decrease	Large decrease	Small or large decrease	Within normal range or small decrease‡	Large decrease	Large decrease	Large decrease
$R_{rs}$	Within normal range or slightly increased	Usually increased	Increased	Within normal range or increased			
Extension of pathological process	Diffuse	Diffuse	Diffuse	Variable	Diffuse	Diffuse	Diffuse
Origin¶	Direct or indirect	Direct or indirect	Indirect	Direct	Direct	Direct	Direct

This list of neonatal respiratory conditions should be considered illustrative, because other disorders could share pathophysiological traits with ARDS. ARDS=acute respiratory distress syndrome. MAS=meconium aspiration syndrome.  $C_{rs}$ =respiratory system compliance.  $R_{rs}$ =respiratory system resistance. \*Pneumonia refers to any type of infectious or biliary pneumonia following intrahepatic cholestasis of pregnancy. †Aspiration refers to lung injuries related to the aspiration of material other than meconium (eg, maternal blood, milk, gastric or bile secretions, and water in the case of underwater birth). ‡Changes in compliance can vary depending on the extension of the pathological process. § $R_{rs}$  is usually within the normal range or slightly increased in ARDS and paediatric ARDS, however underlying obstructive conditions (eg, bronchopulmonary dysplasia) or concomitant airway inflammatory diseases (eg, bronchiolitis) might change these resistances. ¶Origin refers to the triggers occurring directly (eg, neonatal aspiration syndromes and pneumonia) or indirectly in lung tissue (eg, sepsis and necrotising enterocolitis).

**Table 1: Neonatal ARDS respiratory disorders that share similar physiopathology with ARDS and paediatric ARDS**

Although clinicians are aware of the possible existence of ARDS in neonates, it remains unclassified as an entity. The need to establish an entity to define neonatal ARDS acknowledges important differences between neonates and adults. Neonatal lungs continue to undergo alveolarisation and thus neonates have fewer alveoli than adults. Developmental arrest, including features of bronchopulmonary dysplasia, might present in lungs of neonates due to previous insults and therapies. The chest wall is more compliant, the insertion and structure of the diaphragm differs from adults, and the diaphragm contributes more to tidal ventilation in neonates than in adults—tidal ventilation in neonates uses smaller tidal volumes and higher frequencies.

Both innate and acquired immunity are subject to extensive modifications during fetal life and in the perinatal period,<sup>29</sup> and preterm neonates have increased susceptibility to infectious agents. Neonates also have different comorbidities or pre-existing conditions.

Specific characteristics of neonates might affect the epidemiology, clinical course, and prognosis of neonatal ARDS. The triggers and characteristics of neonatal ARDS might be different from those of other ages, similar to the differences that have been observed between paediatric and adult ARDS for infectious triggers, incidence, and mortality.<sup>30</sup> These differences highlight that treatment of ARDS in neonates might be different and further justify the need for a specific neonatal ARDS definition.

### Biological, pathophysiological, and histological rationale for neonatal ARDS

ARDS is biologically characterised by qualitative or quantitative surfactant dysfunction affecting both proteins and phospholipids, and extensive lung tissue inflammation.<sup>31,32</sup> These biological processes share commonality with a number of neonatal respiratory

disorders characterised by variable secondary impairment of surfactant function or surfactant amount, rather than primary surfactant deficiency. For instance, meconium aspiration syndrome, biliary pneumonia, and respiratory failure following severe chorioamnionitis or sepsis are examples of severe neonatal respiratory disorders.<sup>33–38</sup> Like ARDS, secondary impairment of endogenous surfactant and inflammation of the lung in these disorders explain the limited and often transient response to exogenous surfactants.<sup>39,40</sup> This secondary impairment of surfactant is probably due to secretory phospholipase A2, which triggers the inflammatory cascade and hydrolyses surfactant phospholipids in these neonatal disorders and ARDS in older children and adults.<sup>32,33,41</sup> This phenomenon might also occur in preterm neonates in addition to pre-existing pathophysiology such as insufficient alveolarisation, impaired surfactant function, and quantitative surfactant deficiency.<sup>37,38</sup> Figure 1 illustrates the interplay between biological mechanisms and surfactant in neonatal conditions similar to ARDS in older children and adults. A more extensive list of biological mechanisms in these neonatal respiratory disorders is available in the appendix.

Table 1 summarises the pathophysiological similarities between specific neonatal respiratory disorders, which are traditionally considered distinct entities, with unrelated triggers, but each shares similarities when considered within the pathophysiological framework of ARDS. Like ARDS, these conditions can be triggered by either direct injury to the lung parenchyma (ie, direct or primary ARDS) or by an extrapulmonary process (ie, indirect or secondary ARDS), such as sepsis, necrotising enterocolitis, perinatal asphyxia, or biliary pneumonia following obstetric cholestasis.<sup>42</sup> The common physiopathological cascade of these neonatal disorders is summarised in figure 2.

It includes augmented alveolar surface tension, which increases elastic recoil and decreases compliance, causing heterogeneous atelectasis.<sup>31</sup> This process is often accompanied by intrapulmonary right-to-left shunt and ventilation or perfusion mismatching, exacerbating hypoxaemia. Neonates with these disorders might also have more complex shunts through the foramen ovale or ductus arteriosus,<sup>43,44</sup> and potentially increased airway resistance.<sup>45,46</sup> Moreover, the framework of ARDS offers potential in the understanding of acute-on-chronic respiratory failure in neonates, such as the preterm infant with evolving bronchopulmonary dysplasia, who develops, for instance, aspiration, pneumonia, or bronchiolitis. Unlike neonatal RDS, ARDS definitions allow for the complex, low compliance, and high resistance states that are characteristically present in infants with ARDS and bronchopulmonary dysplasia.<sup>8,45,46</sup> Finally, a generalised systemic inflammatory response and secondary multi-organ failure related to the need for aggressive mechanical ventilation<sup>47</sup> is commonly associated with both ARDS and severe neonatal respiratory disorders.<sup>48</sup>

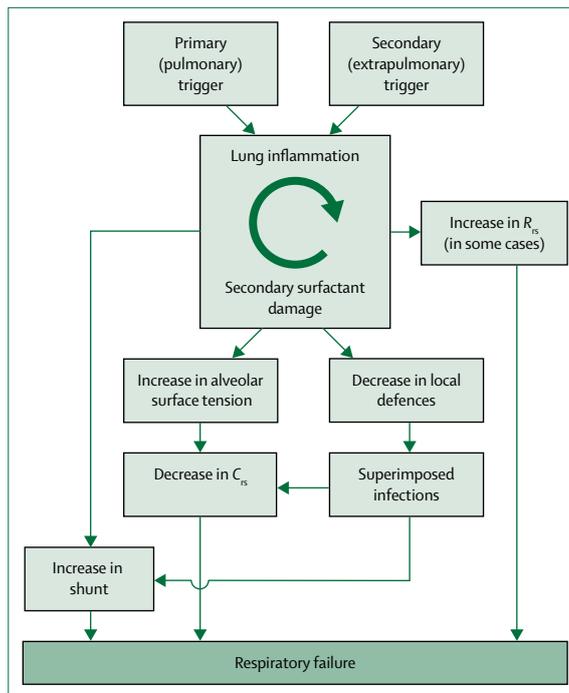
The histological sign of the acute phase of ARDS, occurring before the insurgence of extensive fibrosis, is diffuse alveolar damage,<sup>1,49</sup> which is characterised by interstitial and alveolar haemorrhage or inflammatory oedema, cellular infiltration, and atelectasis with possible formation of hyaline membranes.<sup>50</sup> Diffuse alveolar damage is associated with meconium,<sup>51</sup> milk,<sup>52</sup> or water aspiration after underwater birth,<sup>53</sup> sepsis and infectious pneumonia,<sup>54,55</sup> pulmonary haemorrhage,<sup>56</sup> perinatal asphyxia complicated by severe respiratory failure,<sup>57</sup> and biliary pneumonia.<sup>58</sup>

The biological, pathophysiological, and histological similarities between ARDS and some neonatal respiratory disorders, including those that occur during the perinatal period, provide a strong rationale for defining these disorders as neonatal ARDS.

### Methods used in the Neonatal ARDS Project

An international multidisciplinary collaborative project commenced in January, 2014, with the aim to draft and test a definition for neonatal ARDS. The project method is summarised in figure 3. Experts in respiratory critical care from neonatal and paediatric intensive care units representing ESPNIC, ESPR, and independent expert colleagues, were contacted to create a Steering Committee composed of 12 members. Experts were selected after discussion in ESPNIC and ESPR Councils, on the basis of their research in paediatric and neonatal critical respiratory care over the past 10 years. Because respiratory medicine is a niche area of neonatal critical care, experts were not chosen systematically and the Steering Committee size was decided by convenience sampling.

The Steering Committee regularly communicated via email or teleconference supported by an ESPNIC administrative secretariat. Face-to-face meetings were

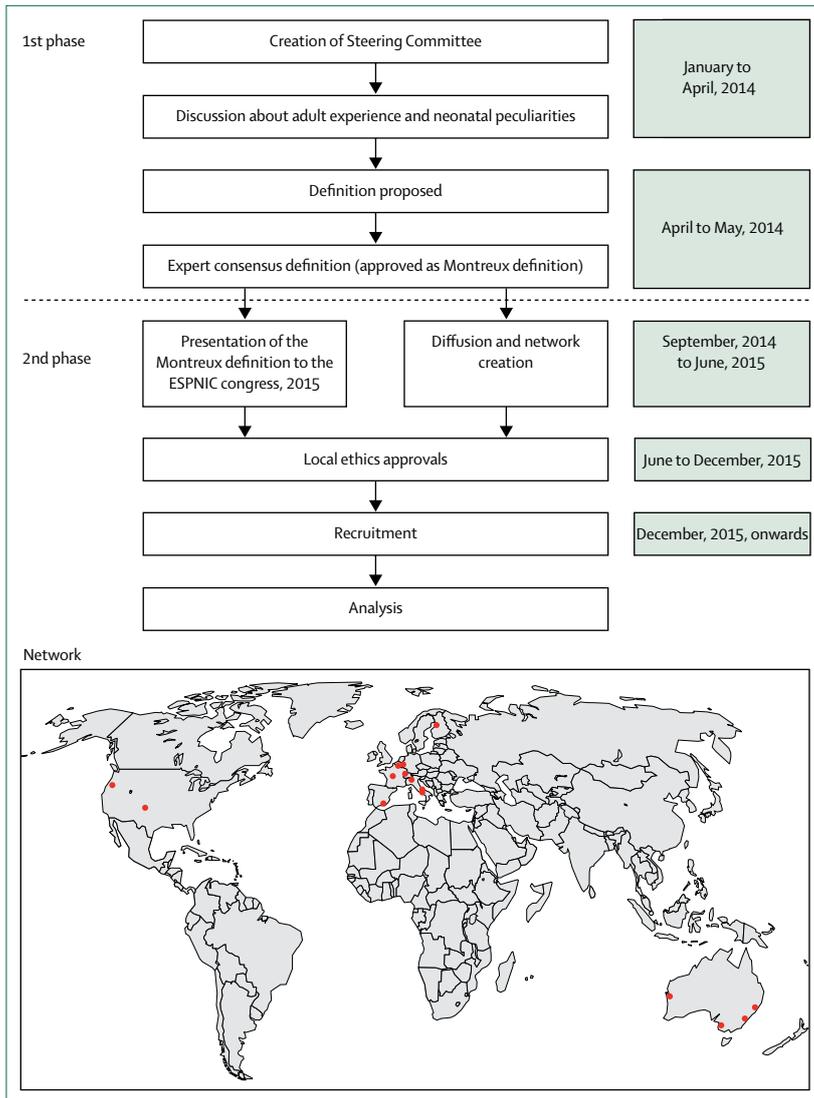


**Figure 2: Pathophysiological cascade of neonatal ARDS**

Typical pulmonary triggers include local infection, biliary pneumonia, bronchiolitis, and aspiration of meconium, blood, water, milk, bile, or gastric secretion; typical extrapulmonary triggers include sepsis or systemic inflammatory conditions (eg, fetal inflammation, chorioamnionitis, necrotising enterocolitis, or perinatal asphyxia). All triggers activate the inflammation-surfactant damage cycle (lung inflammation causes secondary surfactant damage, which causes lung inflammation). Right-to-left shunt can be intrapulmonary or extrapulmonary because of the possible presence of a patent ductus arteriosus or foramen ovale.  $C_s$ =respiratory system compliance.  $R_{rs}$ =respiratory system resistance.

also held in conjunction with the Paediatric Academic Societies and the European Academy of Paediatric Societies congresses. The Neonatal ARDS Project has received ESPNIC and ESPR endorsements following appropriate internal procedures. One author, GC, an expert in adult critical care, was also consulted and participated in the discussions regarding ARDS definition, biology, and physiopathology, but was not involved in meetings about the consensus on the neonatal ARDS definition.

The Committee used a Quaker-based consensus technique,<sup>59</sup> which included open discussions with active listening and sharing of information and questions, with resulting ideas and solutions attributed to the whole group.<sup>59,60</sup> A vote on any particular point was not needed, because, after the discussions, unanimity was reached on every point of the definition. Moreover, the Steering Committee members had previously collaborated on other projects or knew each other, thus no personal influences were evident. The Quaker technique can increase the time taken to reach a consensus—the time allocated to this phase of the Neonatal ARDS Project was sufficient to enable



**Figure 3: The Neonatal ARDS Project: workflow and centres involved in the network (as per November, 2016)**  
The network includes two coordinating centres including South Paris University Hospitals (Medical Center "A.Beclere", Paris, France) and University of Western Australia (Perth, Australia) and participating centres (appendix) according to November, 2016.

everybody to express their ideas and exchange information from a multidisciplinary perspective.

We acknowledge that this method could present some substantial limitations—such as the influence of strong opinions, lack of anonymity, or various external factors—compared with other consensus techniques. This approach can also cause less dominant members of the group to agree on matters rather than offer a different opinion. However, we believe that the duration of discussions partly reduced the effect of these limitations on the outcome and the technique was the most suitable for a cross-disciplinary group discussion.

According to the most recent ARDS definition,<sup>12</sup> we used a series of basic criteria to create a definition of

neonatal ARDS: acute onset; oxygenation impairment with reduced end expiratory lung volume requiring positive pressure to recruit the alveoli; respiratory failure not fully explained by lung oedema due to heart failure; and diffuse bilateral opacities with loss of aeration on chest radiographs.<sup>12</sup> On the basis of these criteria, the following neonatal respiratory disorders would qualify for a diagnosis of ARDS: meconium, milk, bile, blood, or water aspiration, lung haemorrhage, and infectious or biliary pneumonia. We also identified acute processes occurring in extrapulmonary organ systems that might trigger acute respiratory failure via systemic inflammatory responses and thus meet ARDS criteria, such as early-onset or late-onset sepsis, fetal inflammation, perinatal asphyxia, and necrotising enterocolitis.<sup>61</sup>

### The Montreux definition of neonatal ARDS

The Committee maintained consistency in ARDS<sup>12</sup> and paediatric ARDS<sup>17</sup> definitions where possible. Table 2 shows the final Montreux definition of neonatal ARDS, which was approved by consensus of the Steering Committee at a meeting in Montreux (Switzerland). The following ten points addressed in this Committee meeting should be highlighted. First, the definition of neonatal ARDS applies to infants from birth until 44 weeks, post-menstrual age or until 4 weeks, postnatal age (for neonates born after 40 weeks, post-menstrual age) to account for the role of prematurity; ARDS in infants older than these age limits should be diagnosed according to PALICC definition.<sup>17</sup> Second, all five criteria listed in table 2 should be met for neonatal ARDS to be diagnosed and third, provided that all five criteria are fulfilled, no thresholds for birthweight or gestational age exist. The fourth point to highlight is that neonatal ARDS might be triggered by perinatal conditions discussed in this Position Paper, however, these triggers are not exhaustive; other conditions could trigger ARDS and be revealed in the second phase of the Neonatal ARDS Project. The fifth point is that the Montreux definition includes neonates on any type of respiratory support; those receiving invasive and non-invasive ventilation might also qualify for ARDS diagnosis.

The three following conditions specific to the neonatal period, which each have a different pathophysiology of ARDS, constitute the exclusion criteria for the diagnosis of neonatal ARDS and cover the sixth point addressed: (1) congenital anomalies (eg, pulmonary adenomatous malformation, sequestration, or diaphragmatic hernia), which usually have easily recognisable imaging and clinical features; (2) genetic disorders of the surfactant system, which are rare anomalies and might clinically present in a similar manner to ARDS<sup>62</sup> (in some cases, specific genetic investigations might be needed to rule out these conditions); and (3) RDS and transient tachypnoea of the neonate, which are distinct entities with their own biology (table 2). The mandatory criteria

for diagnosis of RDS are respiratory distress appearing within the first 24 h of life, with complete, sustained, and prompt response to surfactant or lung recruitment or both; additional non-mandatory criteria are lung imaging supporting the diagnosis or lamellar body counts  $\leq 30\,000/\text{mm}^3$ , or both. The mandatory criteria for TTN diagnosis are mild (Silverman score  $\leq 3$ ) respiratory distress appearing within the first 24 h of life and resolving within the first 72 h of life, needing treatment only with supplemental oxygen or nasal continuous positive airway pressure or both; additional non-mandatory criteria are lung imaging supporting the diagnosis or lamellar body counts  $>30\,000/\text{mm}^3$ , or both.

The next point to raise is that a neonatal ARDS diagnosis requires the presence of diffuse, bilateral, irregular opacities, infiltrates, or complete opacification of the lungs, which are not fully explained by the conditions representing the exclusion criteria. Similar to ARDS in older children and adults, opacities or infiltrates do not have to involve all four lung quadrants, but localised processes causing acute hypoxic respiratory failure, such as focal pneumonia or bronchiolitis, do not qualify as ARDS.<sup>6</sup> Chest radiographs from patients with ARDS that fulfil the Montreux definition, similar to the process used for the Berlin definition,<sup>12</sup> are in the appendix. The use of radiographs and scans has been shown to improve the accuracy of ARDS diagnosis.<sup>63</sup> The images show the most common possible triggers discussed during the project meetings (appendix). Radiographs were circulated within the Steering Committee and all panellists unanimously agreed on the ARDS diagnosis. Other imaging techniques, such as CT scans and lung ultrasound are not always available, thus images using these techniques are not provided. However, these imaging techniques should be used in clinic if available and sufficient clinical expertise exists for their interpretation.

The eighth point to highlight is that in order to simplify the evaluation and diagnosis of ARDS across the paediatric ages, oxygenation impairment is assessed with the same oxygenation index concentrations as in the PALICC definition.<sup>17</sup> This definition stipulates oxygenation index thresholds of 4.0–7.9 for mild ARDS, 8.0–15.9 for moderate ARDS, and 16.0 or higher for severe ARDS.<sup>17</sup> For neonates treated with non-invasive respiratory support, accurate mean airway pressure calculation is difficult. Estimations of the applied mean airway pressure should only be made when the airway leak has been minimised, which can be achieved by closure of the mouth with gentle pressure on the jaw and use of interfaces of appropriate size.<sup>64,65</sup> Blood gas values from indwelling arterial lines should be used to calculate oxygenation index. However, obtaining arterial samples might be difficult in some neonates; transcutaneous oxygen tension is a reliable alternative measurement.<sup>66–82</sup> Thus, transcutaneous values are allowed in the calculation of oxygenation index when arterial values are unavailable, and these values should be obtained under appropriate

	Details
Timeframe	Acute onset (ie, within one week) from a known or suspected clinical insult
Exclusion criteria	RDS, TTN, or congenital anomalies as a primary current acute respiratory condition
Lung imaging	Diffuse, bilateral, and irregular opacities or infiltrates, or complete opacification of the lungs, which are not fully explained by local effusions, atelectasis, RDS, TTN, or congenital anomalies
Origin of oedema	Absence of congenital heart disease explaining the oedema (this includes ductus arteriosus with pulmonary overflow if no acute pulmonary haemorrhage exists). Echocardiography is needed to verify the origin of oedema.
Oxygenation deficit expressed as OI*	Mild ARDS: $4 \leq \text{OI} < 8$ Moderate ARDS: $8 \leq \text{OI} < 16$ Severe ARDS: $\text{OI} \geq 16$

ARDS=acute respiratory distress syndrome. RDS=respiratory distress syndrome. TTN=transient tachypnoea of the neonate. OI=oxygenation index. \*OI can be calculated by use of arterial or, if arterial values are unavailable, transcutaneous oxygen tension values, with appropriately calibrated transcutaneous devices. In the case of persistent pulmonary hypertension of the neonate and patent ductus arteriosus, preductal PaO<sub>2</sub> values should be used. The definition applies from birth until 44 weeks, post-menstrual age or until 4 weeks, postnatal age (for neonates born after 40 weeks, post-menstrual age). For the syndrome to be defined all criteria must be fulfilled. OI should be calculated with the most accurate measures available. The syndrome can be diagnosed at any gestational age or birthweight, provided that congenital lung anomalies, RDS, and TTN are excluded as primary respiratory disorder. Criteria for the diagnosis of RDS and TTN, exclusion criteria for neonatal ARDS, and suggestions to improve the reliability of transcutaneous blood gas measurements are provided in the Montreux definition of neonatal ARDS section.

**Table 2: The Montreux definition of neonatal ARDS**

conditions according to the American Association of Respiratory Care clinical practice guidelines<sup>83</sup> and the manufacturers' specific recommendations.

The ninth point to highlight is that SpO<sub>2</sub> concentration is not used to evaluate oxygenation in neonates in the Montreux definition because of the wide variations in fetal haemoglobin concentrations<sup>23,24</sup> and transfusion policies across neonatal intensive care units,<sup>84–87</sup> the possible need for blood transfusions, and the uncertainty in what the target SpO<sub>2</sub> is.<sup>88,89</sup> These factors can affect the oxygen dissociation curve and clinical evaluation in neonates, thus the use of oxygen saturation index or the SpO<sub>2</sub>-to-FiO<sub>2</sub> ratio is not advised.

The last point to address is that persistent pulmonary hypertension in neonates is a well established complication of several disorders in the ARDS spectrum (eg, meconium aspiration syndrome, perinatal asphyxia, sepsis, or congenital pneumonia).<sup>90</sup> Similar to children and adults with ARDS and pulmonary hypertension,<sup>91</sup> persistent pulmonary hypertension might worsen hypoxaemia in neonates with ARDS due to either intrapulmonary or extrapulmonary shunts. In neonates who have persistent pulmonary hypertension and patent ductus arteriosus, preductal PaO<sub>2</sub> should be used to calculate their oxygenation index. The American Association of Respiratory Care guidelines consider

### Search strategy and selection criteria

We searched the authors' personal files and references, PubMed, and Google Scholar for the terms ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonate"[All Fields]) AND "ARDS"[All Fields] OR "acute respiratory distress syndrome" or "acute lung injury"[All Fields]), with no restriction on language or date. This search was last done on Sept 12, 2016. We also searched the Pediatric Academic Societies meetings' abstracts' online archive for the same terms. Non peer-reviewed papers were not included.

transcutaneous values of PaO<sub>2</sub> more accurate if devices are calibrated at 44°C.<sup>83</sup> This might imply some risk of skin injury in the extremely preterm neonates and a short application (for 10–15 min) or a lower temperature calibration might be advised. Conversely, damaged skin areas must always be avoided and factors affecting reliability of transcutaneous measure should be considered.<sup>83</sup> The presence of both persistent pulmonary hypertension and neonatal ARDS does not change the Montreux definition criteria, but instead requires treatment with nitric oxide according to clinical practice guidelines.<sup>92</sup> Further pulmonary vasodilators or extracorporeal life support should also be considered, when necessary.

### Next steps

The Neonatal ARDS Project is divided into two main phases (figure 3). The first phase aimed to review the available literature to create a definition of neonatal ARDS based on an expert consensus of the available scientific knowledge: this phase led to the Montreux definition. This definition has now been or is being presented at ESPNIC, ESPR, and local congresses in order to identify health-care professionals from neonatal and paediatric intensive care units who are willing to participate in the second phase of the project. The second phase consists of a prospective, multicentre, international, web-based, cohort study in which neonates who fulfil the Montreux definition are enrolled in order to: describe the epidemiology, clinical course, and prognosis of neonates affected by neonatal ARDS; identify a list of risk factors for neonatal ARDS, as it exists for adults and older children with ARDS; and guide future studies. Because this study is the first on a newly defined condition, a formal sample size calculation is not possible and it will enrol a convenience sample size of at least 220 neonates presenting with respiratory failure meeting the Montreux definition of neonatal ARDS. This convenience sample size seemed appropriate because a similar population was enrolled to validate the Berlin definition in infants.<sup>14</sup> To date, 15 centres have received local ethics approval including intensive care units that are not affiliated with

the Steering Committee members. The study is coordinated by the South Paris University Hospitals (Paris, France) and the University of Western Australia (Perth, Australia) and recruitment began in December, 2015. Although we cannot foresee any particular amendments to the Montreux definition arising from the prospective study, on its completion the Steering Committee will use the findings to reassess the definition and, if appropriate, define the clinical, epidemiological, and pathophysiological subgroups of neonatal ARDS.

### Conclusions

With the dissemination of the Montreux definition of neonatal ARDS, we expect an increase in the clinical attention to the entity of the disorder. The Montreux definition might foster neonatal ARDS research, which will facilitate the investigation of new therapeutic approaches, such as larger or multiple dosing of exogenous surfactants and anti-inflammatory or surfactant protective agents.<sup>93,94</sup> The knowledge that will be acquired in this area might also be useful in the clinical care and research in ARDS in children and adults. Moreover, supporting evidence of the prevalence and incidence of neonatal ARDS will prompt the implementation of health-care policies.

### Contributors

DDL, AHvK, DGT, SEC, OD, VPC, LJZ, MCJK, PT, JB, JJP, and PCR are members of the Neonatal ARDS Steering Committee and participated in all project phases. They all did a personal literature search and contributed to the study design. GC participated in the discussion on adult ARDS definitions and physiopathology and did the relative literature search. Additionally, DDL, AHvK, SEC, MCJK, JJP, and PCR prepared the first draft for the Montreux definition. DDL wrote the first manuscript draft and revised it with AHvK, DGT, SEC, VPC, OD, JJP, and PCR. DDL, OD, and PCR did a specific literature search of clinical cases or animal studies labelled as neonatal ARDS. LJZ, JB, and PT coordinated the internal process and discussions regarding ESPNIC and ESPR endorsement. All authors critically revised the paper for important contents and approved the final version.

### Declaration of interests

We declare no competing interests.

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