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Commentary

Respiratory distress in the neonate: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data

Leigh R. Sweet [a], Cheryl Keech [b], Nicola P. Klein [c], Helen S. Marshall [d], Beckie N. Tagbo [e], David Quine [f], Pawandeep Kaur [g], Ilia Tikhonov [h], Muhammad Imran Nisar [i], Sonali Kochhar [j,l,2], Flor M. Muñoz [k,*], For the Brighton Collaboration Respiratory Distress in the Neonate Working Group [1]

[a] St. Mary's Regional Medical Center, United States
[b] Pharmaceutical Product Development, United States
[c] Kaiser Permanente Vaccine Study Center, United States
[d] Women's and Children's Health Network and Robinson Research Institute and School of Medicine, University of Adelaide, South Australia, Australia
[e] Institute of Child Health & Department of Paediatrics, University of Nigeria Teaching Hospital, Nigeria
[f] Simpson's Centre for Reproductive Health, Royal Infirmary Edinburgh, Scotland, United Kingdom
[g] Clinical Development Services Agency, India
[h] Sanofi Pasteur, United States
[i] Aga Khan University, Pakistan
[j] Global Healthcare Consulting, India
[k] Baylor College of Medicine, United States
[l] Erasmus University Medical Center, Rotterdam, The Netherlands

1. Preamble

1.1. Need for developing case definitions and guidelines for data Collection, Analysis, and presentation for respiratory distress in the neonate as an adverse event following maternal immunization

Definition of respiratory distress in the neonate

Every year, an estimated 2.9 million babies die in the neonatal period (the first 28 days of life), accounting for more than half of the under-five child deaths in most regions of the world, and 44% globally [1]. The majority (~75%) of these deaths occur in the first week of life, with the highest risk of mortality concentrated in the first day of life [2]. Ninety-nine percent of neonatal deaths occur in low- and middle-income countries; south-central Asian countries experience the highest absolute numbers of neonatal deaths, while countries in sub-Saharan Africa generally have the highest rates of neonatal mortality [2].

Respiratory distress is one of the most common problems neonates encounter within the first few days of life [3]. According to the American Academy of Pediatrics, approximately 10% of neonates need some assistance to begin breathing at birth, with up to 1% requiring extensive resuscitation [4]. Other reports confirm that respiratory distress is common in neonates and occurs in approximately 7% of babies during the neonatal period [3,5]. Respiratory disorders are the leading cause of early neonatal mortality (0–7 days of age) [6], as well as the leading cause of morbidity in newborns [7], and are the most frequent cause of admission to the special care nursery for both term and preterm infants [8]. In fact, neonates with respiratory distress are 2–4 times more likely to die than neonates without respiratory distress [9].

Respiratory distress describes a symptom complex representing a heterogeneous group of illnesses [3]. As such, respiratory distress is often defined as a clinical picture based on observed signs and symptoms irrespective of etiology [7,10]. Clinical symptoms most commonly cited as indicators of respiratory distress include tachypnea [3,7–8,10–17], nasal flaring [3,7–8,10–15,17], grunting [3,7–8,10–17], retractions [3,7–8,10–17] (subcostal, intercostal, supracostal, jugular), and cyanosis [3,7–8,10–11,13,17]. Other symptoms include apnea [3,8], bradypnea [8], irregular (seesaw) breathing [8], inspiratory stridor [3,16], wheeze [16] and hypoxia [8,14].

Tachypnea in the newborn is defined as a respiratory rate of more than 60 breaths per minute [12,15], *bradypnea* is a respiratory rate of less than 30 breaths per minute, while *apnea* is a cessation of breath for at least 20 s [18]. Apnea may also be defined as cessation of breath for less than 20 s in the presence of bradycardia or cyanosis [18]. *Nasal flaring* is a compensatory symptom that is caused by contraction of alae nasi muscles, increases upper air-

* Corresponding author at: Baylor College of Medicine, Houston, TX, United States.
E-mail address: contact@brightoncollaboration.org (F.M. Muñoz).
[1] Brighton Collaboration homepage: http://www.brightoncollaboration.org.
[2] Present address: University of Washington, Seattle, USA.

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way diameter and reduces resistance and work of breathing [8,12,15]. *Stridor* is a high-pitched, musical, monophonic inspiratory breath sound that indicates obstruction at the larynx, glottis, or subglottic area [15]. *Wheezing* is a high-pitched, whistling, expiratory, polyphonic sound that indicates tracheobronchial obstruction [15]. *Grunting* is an expiratory sound caused by sudden closure of the glottis during expiration in an attempt to increase airway pressure and lung volume, and to prevent alveolar atelectasis [8,12,15]. *Retractions* occur when lung compliance is poor or airway resistance is high, result from negative intrapleural pressure generated by contraction of the diaphragm and accessory chest wall muscles, and are clinically evident by the use of accessory muscles in the neck, rib cage, sternum, or abdomen [8,15]. Finally, *cyanosis* is assessed by examining the oral mucosa for blue or gray discoloration and suggests inadequate gas exchange, while *hypoxemia* is signified by an oxygen saturation of less than 90% after 15 min of life [8].

Pathophysiology of respiratory distress in the neonate

Most causes of respiratory distress result from an inability or delayed ability of a neonate's lungs to adapt to their new environment [14]. In utero, the lungs are fluid filled, receive less than 10–15% of the total cardiac output, and oxygenation occurs through the placenta [8,19–21]. For the neonate to transition, effective gas exchange must be established [8,22], alveolar spaces must be cleared of fluid and ventilated [20,21], and pulmonary blood flow must increase to match ventilation and perfusion [14,23]. A small proportion of alveolar fluid is cleared by Starling forces and vaginal squeeze [14,23], however the overall process is complex, and entails rapid removal of fluid by ion transport across the airway and pulmonary epithelium [8,20,23]. Peak expression of these ion channels in the alveolar epithelium is achieved at term gestation, leaving preterm infants with a reduced ability to clear lung fluid after birth [14]. If ventilation or perfusion is inadequate, the neonate develops respiratory distress [14,23].

In utero, high pulmonary vascular resistance directs blood from the right side of the heart through the ductus arteriosus into the aorta [8]. When the umbilical vessels are clamped at birth the low-resistance placental circuit is removed, systemic blood pressure is increased, and the pulmonary vasculature relaxes [8,20]. Expansion of the lungs and increase in PaO2 results in increased pulmonary blood flow and constriction of the ductus arteriosus [8,21]. Cardiopulmonary transition is completed after approximately 6 h [8]. The neonate's respiratory pattern may initially be irregular, but soon becomes rhythmic at a rate of 40–60 breaths per minute [8]. A neonate's first breaths tend to be deeper and longer than subsequent breaths [19], they are characterized by a short deep inspiration followed by a prolonged expiratory phase [24]. This breathing pattern helps the neonate develop and maintain functional residual capacity [24].

Causes of respiratory distress in the neonate

Respiratory distress may be the clinical presentation of numerous conditions that affect the neonate (see Table 1). Specific causes of respiratory distress may be difficult to ascertain based on clinical presentation alone. The most common causes of respiratory distress in the newborn are pulmonary in origin and include transient tachypnea of the newborn, respiratory distress syndrome, meconium aspiration syndrome, pneumonia, sepsis, pneumothorax, persistent pulmonary hypertension of the newborn, and delayed transition [13]. Extrapulmonary etiologies, such as congenital heart defects, airway malformations, inborn errors of metabolism, neurologic, and hematologic causes are less common [13].

Transient Tachypnea of the Neonate (*TTN*) is the most common etiology of respiratory distress in the neonatal period [8,13]. TTN occurs in near-term, term and late preterm infants, and affects 3.6–5.7 per 1000 term infants, and up to 10 per 1000 preterm infants [8,17]. TTN is a result of delayed resorption and clearance of alveolar fluid from the lungs [5,13]. Following delivery, the release of prostaglandins distends lymphatic vessels which remove lung fluid as pulmonary circulation increases following the first fetal breath [13]. Cesarean section prior to the onset of labor bypasses this process, and is therefore a risk factor for TTN [8,13,17]. Other risk factors include surfactant deficiency [13], maternal asthma, diabetes, prolonged labor, and fetal distress requiring maternal anesthesia or analgesia [8,17,25]. TTN presents within the first two hours after birth and can persist for up to 72 h [13]. Clinical presentation includes rapid, shallow breathing with occasional grunting or nasal flaring [17], and rarely respiratory failure [8]. Breath sounds may either be clear, or reveal rales on auscultation [13]. TTN is generally a self-limited disorder [5], however, the higher the initial respiratory rate, the longer TTN is likely to last [13].

Respiratory Distress Syndrome (*RDS*) is seen soon after birth, and worsens during the first few hours of life [8,17]. RDS occurs because of surfactant deficiency or dysfunction resulting in increased alveolar surface tension and alveolar collapse at the end of expiration [8,17]. The disease progresses rapidly [13], with increased work of breathing, intrapulmonary shunting, ventilation perfusion mismatch, and hypoxia with eventual respiratory failure [8,17]. The risk of RDS is inversely proportional to gestational age; RDS occurs in approximately 5% of near-term infants, 30% of infants less than 30 weeks gestational age, and 60% of premature infants less than 28 weeks gestational age [8,17]. Additional factors associated with development of RDS are male sex in Caucasians, infants born to mothers with diabetes, perinatal asphyxia, hypothermia, multiple gestations, cesarean delivery without labor,

Table 1
Etiologies of respiratory distress in the neonate [8,12,13,15,17].

Pulmonary	
Congenital	Pulmonary hypoplasia, congenital diaphragmatic hernia, chylothorax, pulmonary sequestration, congenital cystic adenomatous malformation of the lung, arteriovenous malformation, congenital lobar emphysema, congenital alveolar proteinosis, alveolar capillary dysplasia, congenital pulmonary lymphangiectasis, surfactant protein deficiency
Acquired	Transient tachypnea of the newborn, respiratory distress syndrome, meconium aspiration syndrome, pneumonia, pneumothorax, pneumomediastinum, atelectasis, pulmonary hemorrhage, bronchopulmonary dysplasia, persistent pulmonary hypertension of the newborn, diaphragmatic paralysis, drug reaction, anaphylactic reaction, hypersensitivity syndrome, inhalation exposure
Extrapulmonary	
Airway	Nasal obstruction, choanal atresia, nasal stenosis, micrognathia, Pierre Robin anomaly, cleft palate, macroglossia, glossoptosis, laryngeal stenosis or atresia, tracheal atresia, laryngeal cyst or web, vocal cord paralysis, subglottic stenosis, hemangioma, papilloma, laryngomalacia, tracheobronchomalacia, tracheobronchial stenosis, tracheoesophageal fistula, vascular rings, cystic hygroma and external compression from other neck masses
Cardiovascular	Transposition of the great arteries, tetralogy of fallot, large septal defects, patent ductus arteriosus, coarctation of the aorta, congestive heart failure, cardiomyopathy, pneumopericardium
Hematologic	Polycythemia, anemia, severe hemolytic disease, hypovolemia, hereditary hemoglobinopathies, hereditary methemoglobinemia
Infectious	Sepsis, bacteremia, meningitis
Metabolic	Hypoglycemia, hypocalcemia, hypermagnesemia, hypo- or hypernatremia, inborn errors of metabolism
Neuromuscular	Hypoxic-ischemic encephalopathy, intracranial hemorrhage, hydrocephalus, seizure, narcotic withdrawal, muscle and spinal cord disorders
Thoracic	Skeletal dysplasias
Miscellaneous	Asphyxia, acidosis, hypothermia, hyperthermia, hydrops fetalis