The Respiratory Course of Extremely Preterm Infants: A Dilemma for Diagnosis and Terminology

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Antenatal corticosteroids, postnatal surfactant treatment, and new strategies for respiratory care have modified the clinical presentation, lung outcome, and survival of extremely low birth weight (ELBW) infants. These changes over the last 10-20 years have resulted in a large population of ELBW survivors that have clinical courses that are quite different from those observed before the general use of surfactant and antenatal corticosteroids. The classic definitions and diagnoses for respiratory problems developed for larger preterm infants may not be accurate for this ELBW population. Hence, clinicians often find themselves without the proper terms to describe and code the clinical course in many of these patients.

The Respiratory Course: A History

Before the introduction of mechanical ventilation in the 1960s, many of the preterm infants who died soon after birth with respiratory failure were diagnosed with hyaline membrane disease (HMD) at autopsy. The relatively mature survivors generally recovered with normal pulmonary function. With the introduction of mechanical ventilation, an increasing number of premature infants survived, but many did so with severe lung damage, described initially by Northway et al in 1967 as bronchopulmonary dysplasia (BPD). These infants initially had severe HMD and persistent respiratory failure that evolved into BPD. With increased survival, the term respiratory distress syndrome (RDS) replaced HMD as the clinical diagnosis. With the introduction of surfactant treatment after 1990, and the more widespread use of antenatal corticosteroid therapy after 1994, severe RDS became less frequent. Although after the introduction of these therapies many of ELBW infants needed minimal early respiratory support and had much better respiratory outcomes, they were still managed with mechanical ventilation and often had the default diagnosis of “RDS”.

The Initial Respiratory Diseases of ELBW Infants

One of the diagnostic dilemmas that clinicians face now is what to call the mild initial respiratory course that is observed in many ELBW infants today. The respiratory failure in premature infants immediately after birth can result from poor postnatal adaptation, birth hypoxia causing central respiratory depression, or lung inflammation associated with chorioamnionitis. Although many of these ELBW infants need some form of initial respiratory support and supplemental oxygen, this need may result from retained lung fluid, structural immaturity of the lungs, or insufficient respiratory effort. Ideally, the diagnosis of RDS should be limited to respiratory failure occurring in preterm infants when there are clinical and radiographic findings consistent with surfactant deficiency. However, there is no clinically acceptable way to securely diagnose surfactant deficiency. The RDS diagnosis is imprecise at best because many of these infants are intubated and ventilated shortly after birth and are given surfactant. These interventions can mask the clinical and radiographic signs of RDS. The converse problem is that these infants are frequently diagnosed as RDS, even when they do not have significant lung disease, because they are ventilated. Infants who require respiratory support primarily because of poor respiratory effort, but without significant lung involvement, should be diagnosed as respiratory depression or apnea rather than RDS and should not be routinely treated with surfactant.

A survey of recent clinical experiences will illustrate the diagnostic problems of determining who has RDS and who does not have RDS (Table). The National Institute of Child Health and Human Development Neonatal Research Network reported an incidence of RDS of 63% for infants with birth weights of 500-1000 g for 1997-2002. The diagnosis required oxygen use from 6-24 hours of life, respiratory support to 24 hours, and a chest radiograph consistent with RDS. However, for the more recent interval from 2003-2007 for infants <28 weeks’ gestation (approximately the same population as for the earlier interval), 95% of infants had a diagnosis of RDS because the less stringent criteria of oxygen use or respiratory support for ≥6 hours of the first 24 hours without a chest radiograph requirements were used. These are quite minimal criteria for a diagnosis of RDS in ELBW infants. The variability in the diagnosis of RDS can also result from the use of surfactant treatment as...
a criterion to diagnose RDS.\textsuperscript{5,9-13} Clinicians are re-evaluating the liberal use of noninvasive continuous positive airway pressure (CPAP) as a way to manage RDS and avoid BPD, as first reported in 1987 by Avery et al.\textsuperscript{14} and extensively used in Scandinavia in the 1990s.\textsuperscript{13} The use of early CPAP can stabilize spontaneous ventilation for very low birth weight infants and eliminate the need for surfactant treatment in many of them. Another diagnostic problem is that premature infants are frequently born to mothers with symptomatic or asymptomatic infections (chorioamnionitis),\textsuperscript{15} Is the initial respiratory failure in these infants due to surfactant deficiency, antenatal pulmonary infection/inflammation, or a combination of both? This is a difficult differential diagnosis because the clinical and radiographic manifestations of RDS and pneumonia in this population can be very similar and often both conditions may coexist. The use of tests to evaluate the amount of surfactant in the amniotic fluid has become uncommon, thus, eliminating one of the tools that were available to diagnose RDS. Bacteria or elevated cytokine concentration,\textsuperscript{12,27} damage from mechanical overdistention of the airways with pathogens,\textsuperscript{12,22,31} recurrent focal or segmental atelectasis due to airway obstruction, pulmonary edema because of a patent ductus arteriosus and increased pulmonary blood flow,\textsuperscript{23,33} or secondary surfactant deficiency.\textsuperscript{34} In fact, the dominant variable may be how the processes of lung injury, repair, and growth progress in any given infant, which are variables that cannot be quantified or predicted. This is an area where more research is needed to better define the possible role of the different pathogenic mechanisms.

The problem then is how should the clinician label an ELBW infant who had no, mild, or severe, surfactant treated RDS early after birth, but at 1 to 3 weeks is receiving some respiratory support (CPAP, supplemental oxygen, high flow nasal cannulae, or mechanical ventilation)? RDS is not an appropriate diagnosis after the first week. The infant may still have a patent ductus arteriosus that has not closed, the airway might be colonized with several pathogens with or without other signs of systemic infection, and the chest radiographs show diffuse haziness with some patchy areas of higher densities that could represent segmental atelectasis or pneumonia or recurrent focal or segmental atelectasis due to airway obstruction, pulmonary edema because of a patent ductus arteriosus and increased pulmonary blood flow, or secondary surfactant deficiency. In fact, the dominant variable may be how the processes of lung injury, repair, and growth progress in any given infant, which are variables that cannot be quantified or predicted. This is an area where more research is needed to better define the possible role of the different pathogenic mechanisms.
and a low PaO2, but is considered to have normal lung function pending respiratory failure with tachypnea, a high PaCO2, 92% breathing room air (PaO2 45 mm Hg) may have impending respiratory failure with tachypnea, a high PaCO2, and a low PaO2, but is considered to have normal lung function by the neonatal community because there are no good reference values for lung function at different gestational and postnatal ages. If the neonatal community does not have good names for the respiratory syndromes we see, then data bases will be most problematic.

Proposed Terminology

To unify the terminology used to describe these infants we propose the term “respiratory instability of prematurity” (RIP) as a general descriptor for very low birth weight infants requiring some form of respiratory assistance but with multiple factors contributing to their respiratory failure. We suggest using the term “respiratory” rather than “pulmonary” because many of the infants require respiratory support not so much due to their pulmonary disease, but because of inconsistent central respiratory drive and poor inspiratory effort. We propose using the term “instability” rather than “insufficiency” because many of these infants have a poorly defined combination of respiratory control problems, mechanical “instability” as well as lung parenchymal disease that contribute to the respiratory problems, but this is not always accompanied by failure defined by abnormal arterial blood gases. This is a suggested term that can be considered by the neonatology community.

Important contributors to early RIP following birth are respiratory depression and poor respiratory effort, RDS due to surfactant deficiency, pneumonia/inflammation, and pulmonary hypoplasia. The factors that contribute to the transitional RIP in infants who subsequently need prolonged respiratory support were mentioned earlier. The clinical evolution of these infants during this transitional period is extremely variable and unpredictable. Although some of them show gradual improvement and wean from respiratory support and supplemental oxygen before the end of the first month, others have progressive respiratory compromise, remain dependent on oxygen and respiratory support, and are eventually diagnosed with BPD. The diagnosis of BPD currently depends on a demonstration of oxygen need,26,37 but there are multiple factors and pathologies contributing to this oxygen dependence.

The purpose of the proposed terminology, RIP, is not to replace specific diagnoses when they are clear, but to provide clinicians with a more encompassing diagnosis in infants in whom there are several mechanisms contributing to the respiratory failure, but without clear evidence of their relative contribution or importance. A second purpose is to stimulate a discussion of the diagnostic and coding difficulties for respiratory diseases in ELBW infants.

References


Submitted for publication Feb 8, 2012; last revision received Apr 17, 2012; accepted May 23, 2012.
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